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THE UNIVERSITY OF ALBERTA

The Effects of Hippocampal Spreading Depression in Rats on Acquisition and Performance of a Conditioned Emotional Response

by

© Timothy W. Parker

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
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Abstract

Hippocampal spreading depression (HSD) was induced in groups of rats during the preconditioning, conditioning, or testing phases of a latent inhibition paradigm involving a conditioned emotional response (CER). On Test One, all three experimental groups previously given HSD showed a marked impairment in acquisition of the CER. In contrast, two control groups not given HSD showed a relatively high degree of CER acquisition. These results suggest important involvment of the hippocampus in the process of conditioning a CER. A disrupted hippocampus possibly leads to impaired consolidation processes during learning trials.

In addition, the two control groups which showed good acquisition on the first test, were markedly impaired when given HSD on Test Two, and then showed good recovery on Test Three, by which time the effects of HSD had worn off. This demonstration of impairment suggests that the HSD interfered with normal hippocampal function, necessary for performance. The subsequent demonstration of recovery eliminates the alternative explanations of faulty consolidation and faulty retention of the association once stored. It is proposed that the obtained impairment is due to either faulty retrieval processes caused by the HSD, or to intact retrieval processes coupled with faulty behaviour sequencing and switching mechanisms.

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I. Introduction

In recent years the elucidation of the function of the hippocampus has become an increasingly popular target research. There is a growing list of hypotheses which implicate the hippocampus in a wide range of functions, according to the type of research techniques which have been applied. Several approaches have been used in the attempt to discern hippocampal function, ranging from gross lesion and stimulation techniques, to single unit recording. From the application of these and other techniques has arisen a wealth of data which supports a number of widely divergent conclusions. Such a situation is hardly surprising in light of the anatomically central position in the limbic system which the hippocampus occupies, and the fact that it receives direct cortical input via the perforant pathway from the entorhinal cortex. However in spite of the widely divergent findings, and the breadth of behavioural situations studied, most of the evidence to date can be used to support several primary hypotheses concerning hippocampal function, each focussing on a different element of the learning-performance sequence. The experiments to be described represent an attempt to provide evidence which supports one or other of these hypotheses, while eliminating the remainder. In order to clearly define the currently held views on the function of the hippocampus, a review of the pertinent literature is provided, beginning with a discussion of the hippocampal electroencephalogram (EEG) literature.

A. Hippocampal EEG

Much of the initial evidence for the major theories concerning hippocampal function has been provided by attempts to correlate specific hippocampal EEG patterns with distinct categories of overt behaviour. Perhaps one of the most ubiquitous and easily obtained measure of hippocampal activity is the hippocampal theta rhythm (hereafter to be referred to as simply theta). Theta consists of slow, synchronous, high-amplitude waves in the range of four to seven cycles per second, and usually fairly prolonged (Bennett, 1975). According to a review by Kemp and Kaada (1975) theta has been thought to correlate with the following four distinct behavioural functions and activities:

Arousal - Green and Arduini (1954) have reported that theta was most reliably correlated with cortical and behavioural signs of alerting and arousal.

Orienting response - Grastyan, Lissak, Madarasz, and Donhoffer (1959) measured theta during the development of conditioned reflexes and reported that theta was related to movements associated with the tonic orienting behaviour which accompanied the initial stages of learning.

Discrimination learning and attention - Adey, Dunlop, and Hendrix (1960) disagreed with Grastyan *et al* (1959) and maintained that theta was always accompanied by a state of alert attentiveness, not specifically related to overt orienting movements. Instead, Adey *et al* (1960) viewed theta as signifying focussed attention and concluded that theta indicated hippocampal involvement in attention.

Voluntary movement - Vanderwolf (1969) looked at theta in the rat and concluded that theta was not related to alerting or attentive behaviours, but instead was best correlated with 'voluntary' movements, classified by Vanderwolf to mean such activities as walking, running, sniffing, and rearing, as opposed to 'involuntary' movements such as shivering and grooming.

These four conflicting viewpoints invite the question of whether they can be resolved. The main question is whether theta is truly associated with attentive behaviours, and if so do these behavioural states of attentiveness require concomitant somato-motor voluntary movements in order to appear correlated with theta?

This question was addressed by the Kemp and Kaada review (1975) which looked at behaviour in unrestrained cats while recording theta. The categories of behaviour examined were (1) spontaneous and induced changes in level of arousal due to sleep and wakefulness and the transition between the two, (2) orienting responses in a novel environment, and (3) motor acts such as walking, running, drinking, and grooming. Increases in arousal, measured by pupil response, degree of eye opening, and cortical EEG desynchronization, were invariably correlated with increases in theta. In a complementary finding, habituation of arousal led to decreased theta. In waking behaviour theta occurred primarily during tonic orienting responses. In contrast, locomotor activity which was not accompanied by focussed attention was correlated with a marked decrease of theta. Thus the main conclusion reached by Kemp and Kaada (1975) was that in cats theta was primarily dependent on a state of alertness. Also the fact that theta was high for tonic orienting responses provided support for the Grastyan hypothesis mentioned above.

The conclusion concerning the Vanderwolf hypothesis was that it was not supported. Simple voluntary movements which were unaccompanied by high arousal or attentiveness did not correlate with theta. Also animals which freeze in an attentive response show theta, indicating that movement is unnecessary for theta to appear. These findings led Kemp and Kaada (1975) to the following conclusion:

> "the underlying factor common to all behaviours correlated with an increase in hippocampal theta activity is arousal and its control by attentional processes involved in maintaining behaviour 'on-line' with environmental contingencies." (p. 339)

Another attempt to resolve this conflict was reported by Bennett (1975). He concentrated primarily upon the

Adey-Grastyan controversy. Both agreed that theta occurred with attentional activities, but Adey also implicated hippocampal theta in the function of information processing and memory consolidation during learning. As has been mentioned, this disagreement stemmed from the fact that Grastyan found theta only during the early part of learning tasks, while Adey found theta throughout training and overlearning. Bennett (1975) maintained that the differences in electrode placement by the two research teams were not likely to account for the contradicting results. Instead Bennett concluded that the source of the differences was in the learning tasks employed by the two groups and he set out to analyse these. Bennett's results revealed that the modality and mode of presentation of the positive stimulus made no difference. However during a complex task, the appearance of an alerting stimulus prior to the onset of the positive stimulus was correlated with an increase in theta, once again providing evidence that hippocampal theta is integrally involved with attentional processes. Bennett also obtained some other quite interesting findings in these initial investigations. A substantial level of theta was also found during non-reinforced or incorrect responses in a discrimination task. Also theta increased as the subject began to perform better on the task, signified by the decrease of incorrect responses, an event which presumably is correlated with a decreased need to pay as close attention to the task to perform it well.

These results make a valuable contribution towards resolving the Adey-Grastyan controversy in that task complexity accounts for theta appearing only at the beginning of simple tasks, which require only initial focussed attention, and throughout more complex tasks, which require more or less continuous attention to stimuli. Bennett's conclusion (1975) agrees with that of Kemp and Kaada (1975):

> "Theta is related to specific processes of attention to environmental stimuli; processes which the hippocampus presumably mediates." (p. 79)

Thus the general conclusion suggested by the research reviewed above is that tasks requiring attention to environmental stimuli are accompanied by theta, while well-learned tasks, or those dependent response-produced cues (proprioceptive) are accompanied by hippocampal desynchronization.

Bennett (1975) goes on to speculate that perhaps species differences are the reason, or, at any rate, one of the factors, underlying conflicting results in the literature. He mentions that theta is normally the dominant pattern of rats, which Vanderwolf used in his reasearch, while in cats, used by Adey, Grastyan, and Bennett, theta and desynchronization appear to be balanced equally, and theta is much more difficult to record. This suggestion of species differences was originally proposed by Winson (1972) and has received much support from Bennett's subsequent tests, which showed that rat hippocampal theta did not reflect attentional processes. This species specific pattern of theta correlations is even more strikingly demonstrated in primates. Crowne and Radcliffe (1975) report interesting results concerning the appearance of theta in monkeys. Typically monkeys differ from rats and cats in that they exhibit theta much less frequently. Furthermore the appearance of theta in monkeys could not be correlated to any of the experimental situations they were able to devise. These included such things as alarming the monkey by threatening it with an extended pole, and exposing the monkey to novel stimuli in various task settings, all of which most likely produced orienting and attentional responses. The single situation in which theta did appear was discovered serendipitously, in the first few trials of extinction. The striking thing about the Crowne and Radcliffe (1975) results, though, is that they supply strong support for the contention that species differences must be taken into account when analysing theta correlation evidence.

This then is a brief summary of reported research attempting to correlate theta with behavioural events. As has been mentioned, the prime factor in hippocampal theta appearance is the arousal or attention component of behaviour. The question which must now be asked concerns the value of the theta evidence in providing further elucidation of hippocampal function. The evidence discussed above has the major drawback of being only correlational, and, while it is anatomically and physiologically a remote possibility, it is conceivable that theta is completely spurious and does not relate to hippocampal function except in the most indirect of ways. Correlations cannot distinguish between cause and effect, hence it is difficult to arrive at conclusions as to whether theta causes a hippocampal function to occur, or is merely concomitant neural activity.

One way to attempt to answer this problem is to see what happens to the behaviours which have been correlated to theta if theta is abolished. The last part of Bennett's study (1975) deals with this point. Hippocampal theta was abolished by intraperitoneal injection of scopolamine, an anticholinergic drug which has been shown to block hippocampal theta. Stumpf (1965) has shown that scopolamine hydrobromide blocks theta through its action on the pacemaker cells in the medial septal nucleus. Bennett (1975) tested cats, and found them behaviourally unimpaired even at the strongest doses of scopolamine. In addition very small doses were shown to have completely eliminated theta, yet performance remained intact. One point which may be stressed about this study is that it only provides information about the effects of abolishing theta on performance not learning. Also scopolamine produces peripheral side effects which may have confounded the results obtained. These side effects include pupillary dilation and blockage of visual accommodation (Goodman & Gilman, 1965), hence the cats' impaired performance on visual tasks at high dosages may have reflected these perceptual side effects. To control for this, Bennett then injected scopolamine directly into the medial septal nuclei through cannulae. The animals were then monitored throughout learning and performance alike. This technique clearly blocked theta and results showed that for acquisition and performance drugged animals did not differ from controls. This suggests the rather interesting conclusion that perhaps theta is unnecessary in the processes of learning and memory and that it is most likely not a manifestation of an ongoing underlying causal process.

To briefly mention some additional findings bearing on this point, several other researchers have looked at the necessity of theta for behaviour. Their methods include lesion of the septal pacemaker site as well as leaving the tissue intact. Bilateral hippocampal lesion studies (Douglas & Pribram, 1966; Kimble & Pribram, 1963) found no impairment of acquisition rate on a simple two-choice discrimination task. Complementary findings (Thompson, 1969) showed no retention deficits for this type of task. Studies of this nature involving the intact hippocampus by Adey *et al* (1962) yielded inconclusive results. They reported theta-correlated impaired performance in discrimination after sub-thalamic lesions sparing the hippocampus, but the general consensus is that this correlation was spurious, due to motor deficits resulting from damage to the extrapyramidal tract, which is in the area they lesioned. Thus it seems that there is some support at least for the hypothesis that theta is not essential for tasks requiring attention and orienting.

One final pertinent area of research to be reviewed concerns the discovery of which parts of the brain can be stimulated to produce hippocampal theta, and the behavioural correlates exhibited by subjects exposed to such stimulation. Lindsley and Wilson (1975) provided an account of several related studies which looked at brain stem and hypothalamic systems which could influence hippocampal EEG activity and overt behaviour. Initially they reviewed findings by Anchel and Lindsley (1972) of two distinct hypothalamic pathways which, when stimulated, produced opposite patterns of activity in the hippocampus. Stimulation at 100 Hz in the medial posterior hypothalamus elicited hippocampal theta, while stimulation in the lateral posterior hypothalamus produced hippocampal desynchrony. Cryogenic blockade was used to demonstrate that these paths were anatomically distinct.

A variety of evidence, including single unit recording in the septum, led to the conclusion that these influences on the hippocampus are mediated by the septal fornical afferents. Anchel and Lindsley concluded, a conclusion which has been well supported, that the lateral hypothalamic desynchronization system was mediated by the medial forebrain bundle, while the medial theta-producing system was mediated by the dorsal longitudinal fasciculus of Schutz. Both of these pathways innervate the septum, which has been shown to be the site of hippocampal theta pacemaker influence (Petsche, Stumpf, & Gogolak, 1962; Vinogradova, 1975). Additional support comes from Anchel and Lindsley's own work (1972) on septal single unit response to either lateral or medial hypothalamic stimulation.

The discovery of these two distinct systems enabled some quite elegant research involving observation of the behavioural correlates accompanying opposite hippocampal activity in a variety of task situations (Lindsley & Wilson, 1975). To begin with spontaneous hippocampal activity was correlated with spontaneous and task-oriented behaviour alike, and then stimulated changes in hippocampal activity were correlated with overt changes in behaviour. In general, regarding spontaneous hippocampal activity, it was found that theta accompanied behaviours which could be classified as alerting and orienting behaviours, which appeared to involve attention-shifting processes, while desynchrony correlated with fixation of posture and gaze, indicating a process of focussed attention. Similar findings were obtained when stimulation-induced hippocampal rhythms were studied. Lateral stimulation produced desynchrony which was accompanied by an abrupt assumption of a fixed posture and rigid gaze straight ahead. In contrast, medial stimulation produced theta and also alerting and orienting responses. This pattern was even more striking during an operant task, since the animals would suddenly cease to respond when stimulation was applied and either orient or become rigid, depending on the system activated.

The implications of these findings are quite important. This preparation, which allows the reliable elicitation of either theta or desynchrony in the hippocampus, revealed that theta is specifically correlated with behaviours volving attention-shifting processes, while desynchrony correlates with focussed attention. Relating this to the research described earlier on the significance of theta, it provides good support for those studies advocating an attention-shifting role of theta, most notably Green and Arduini (1954) and Grastyan *et al* (1959). An important point must be emphasized here, however. All of the evidence presented still does not preclude the possibility suggested by Bennett's research (1975), that hippocampal theta is simply a concomitant event accompanying behavioural changes, and not a causal one. Certainly the previous discussion of Bennett's work strongly suggests that this is the case. Unfortunately the information regarding the blockade of the hypothalamic systems by cooling reported by Lindsley and Wilson (1975) does not include any behavioural data, so it is impossible to tell whether this method of eliminating theta reveals a causal nature of theta in behavioural change. It is interesting, though, that systems which produce reciprocal effects are so well elaborated.

Further indication of the importance of theta comes from the discovery of other brain sites which, when stimulated, produce hippocampal theta. Green and Arduini

(1959) provided the basis for this work by reporting that high frequency stimulation of the brain stem reticular formation, hypothalamus, intralaminar thalamic nuclei, preoptic area, and septum produced hippocampal theta. Other studies have followed this up and have reported areas in the ventromedial midbrain reticular formation, lateral and anterior hypothalamus, lateral preoptic regions, amygdala, and lateral septum which, when stimulated, produce hippocampal desynchrony. It is interesting, in light of the findings of Anchel and Lindsley (1972), to note that the medial-lateral distinction found in the posterior hypothalamus seems to obtain for the other areas of the brain, most notably the septum, preoptic regions, and the thalamus.

From the preceding it can be seen that controversy exists concerning the importance of hippocampal theta. On the one hand behaviour seems to be relatively unimpaired when theta is eliminated, while on the other compelling evidence that theta is involved in attention-shifting also exists. For this reason, no strong conclusion about theta is possible. Nevertheless the majority of the evidence presented indicates that theta is a neural manifestation of ongoing functions mediated by the hippocampus. Furthermore, it is likely that these functions involve attention-shifting processes.

Thus far it can be seen that most of the evidence concerning hippocampal theta suggests a role of the hippocampus in attentional processes, including orienting. Studies have also been done in an attempt to provide support for other theories of hippocampal function. Bennett and Gottfried (1970) specifically investigated whether theta was reliably correlated with inhibition of a previously reinforced response. Their results were negative, however, forcing them to conclude that hippocampal theta does not reflect a role of the hippocampus in response inhibition. These findings are interesting and relevant in that stimulation-induced theta has been shown to produce a marked inhibition of ongoing activity (Lindsley & Wilson, 1975). The fact that natural occurrences of response inhibition were not accompanied by theta provides some additional support for the hypothesis that stimulation which induced theta may also produce the resulting behaviour shifts through the activation of separate processes not specifically related to theta. However it still appears that for the most part the hippocampal theta literature points to an attention-shifting function of the hippocampus, while little evidence has been found concerning spontaneous theta and response inhibition or memory consolidation processes.

B. Current Theories Of Hippocampal Function

From the preceding discussion it can be seen that there are a variety of suggestions as to the function of the hippocampus arising from the hippocampal EEG literature alone. Further speculations concern all aspects of the learning-performance continuum and all have varying degrees of support. The following is a summary of the most important of these theories.

The Response Inhibition Hypothesis

Evidence that the hippocampus is involved in a response inhibition function is provided by two quite extensive reviews (Douglas, 1972; Izquierdo, 1975) of the results of hippocampal lesion studies. Hippocampally lesioned animals have been found to be markedly impaired in a long list of tasks and abilities including habituation (Leaton, 1965; Leaton, 1967), extinction in operant conditioning (Isaacson, Douglas, & Moore, 1961; Niki, 1962; Jarrard, Isaacson, & Wickelgren, 1964; Jarrard & Isaacson, 1965; Raphelson, Isaacson, & Douglas, 1966; Swanson & Isaacson, 1967; Kimble, 1968) and in classical conditioning (Niki, 1965), initial stages of reversal tasks, successive discrimination (Stein & Kimble, 1966; Jarrard & Lewis, 1967; Hostetter & Thomas, 1967), spontaneous alternation (Roberts, Dember, & Brodwick, 1962; Douglas & Isaacson, 1964; Douglas, Peterson, & Douglas, 1973), and other tasks involving active error reduction. Typically hippocampal animals tend to perseverate (Peretz, 1965; Niki, 1965; Douglas & Pribram, 1966; Brown, Kaufman, & Marco, 1969; Franchina & Brown, 1970) and be quite indistractible (Wickelgren & Isaacson, 1963; Hendrickson & Kimble, 1967). This rather lengthy list of findings contains a common denominator, namely that lesioned animals seem to be unable to adequately change their behaviour when changing environmental circumstances make the existing behaviour irrelevant or even maladaptive. All of the tasks included in the list above involve the inhibition of some ongoing response in order for different, more appropriate, responses to replace them. An important complementary finding which supports this position is that few studies with lesioned animals have reported much impairment in performance if the relevant task is one requiring a simple active response. Kimble (1968) agreed with this hypothesis and suggested that instead of being categorized as having a memory deficit, lesioned animals typically appear unable to forget earlier responses when changing contingencies necessitate such forgetting.

The results of pre-operation training studies are also relevant to the response inhibition hypothesis. If hippocampal ablation produces impairment in performance of tasks learned prior to the ablation, such results would provide strong support for a performance role, such as response inhibition, as opposed to a learning role mediated by the hippocampus. In fact, such results have been reported (Jarrard, 1965; Schmaltz & Isaacson, 1966; Isaacson & Schmaltz, 1968; Schmaltz & Theios, 1972), suggesting that after learning has occurred, damage to the hippocampus produces dramatic performance deficits.

Mediation Of Attention And Orienting Hypothesis

This approach regards the demonstrated lack of ability of lesioned animals to change their behaviour as due to an inability to attend to the environmental changes which necessitate the behavioural changes. Thus an attentional deficit is postulated, rather than one of response inhibition. It should be noted that a result of impaired performance does not allow one to distinguish between these two alternatives, since either would suffice to impair performance.

The origins of this approach are found in the work of Douglas (1972) who suggested that the hippocampus played an attentional role in tuning out non-reinforcing stimulation. According to this hypothesis lesioned animals would be unable to distinguish between reinforcing and non-reinforcing stimulation which impinged upon them, hence they would not exhibit behavioural changes when previously reinforcing stimuli lost their reinforcing properties. This would provide an explanation couched in attentional terms for the lack of extinction and habituation, and also for the presence of other characteristics which demonstrate impaired performance, such as perseveration and indistractibility.

This early hypothesis has been recently reviewed and revised by Solomon and Moore (1975) and their associates. Basically they agree with Douglas (1972) except that they prefer to divide the category of non-reinforcing stimulation into sub-categories of redundant and irrelevant stimulation. Two experimental paradigms, blocking and latent inhibition, were then studied by Solomon (1977) and Solomon and Moore (1975) which test both these sub-categories.

Latent inhibition refers to the phenomenon in which non-reinforced pre-exposure to the conditioned stimulus (CS) retards subsequent conditioning to the CS when it becomes paired to the unconditioned stimulus (UCS). (For a more extensive review of latent inhibition findings see Weiss and Brown (1973).) In this case the stimulus is irrelevant to the subject during the pre-exposure (or pre-conditioning) phase since it signals no consequence. However when lesioned animals are tested in a latent inhibition paradigm they do not show any latent inhibition effect (Ackil, Mellgren, Halgren, & Frommer, 1969; McFarland, Kostas, & Drew, 1978). In other words, it is as if the pre-conditioning had never occurred.

The blocking paradigm neatly tests the category of redundant stimuli. Blocking refers to the fact that when given a rewarded compound stimulus (AX), consisting of a novel element (X) and a previously conditioned element (A), (preferably matched for salience), learning about the novel stimulus is inhibited. In this case, the association formed with the familiar stimulus is said to block the formation of an association with the novel stimulus. (For a review on blocking and some theoretical models of blocking see Mackintosh (1975).) Thus the novel element of the rewarded compound stimulus is redundant, in that it signals no new information, since the subject is already achieving optimal reward. As with latent inhibition, lesioned animals do not show the same results as normals. In blocking lesioned animals show no impairment in learning about the novel, or redundant, stimulus, ie. they do not show blocking (Solomon, 1977; Rickert, Bennett, Lane & French, 1978). An interesting complementary study was also reported by Solomon (1977). Conditioned inhibition involves learning to respond to a single stimulus (A), but to suppress responses when given a compound stimulus (AX). In this task, which, although it involves response suppression, does not require any tuning out of the stimuli to produce a normal result, lesioned animals and normals do not differ. This direct test between response inhibition and attentional deficits provides additional support for the attention theory.

Thus in these specific paradigms it appears that lesioned animals lack an adequate mechanism for determining whether a stimulus is significant to its well-being, or whether it can safely ignore it. More support for this attentional hypothesis comes from the previously discussed hippocampal EEG literature, for it will be remembered that the currently accepted conclusion is that theta manifests an attentive state, although it should be remembered that a final conclusion as to the significance of theta itself is still not available.

Learning Hypothesis

A variety of other types of studies support the contention that the hippocampus is involved in the learning aspect of the learning-performance continuum, specifically in the initial attention to the stimulus contingencies.

Chemical changes, particularly those involving RNA synthesis and protein synthesis increases, have been shown to occur in the hippocampus during learning (Hyden & Lange, 1968; Hyden & Lange, 1970). Nasello and Izquierdo (1969) found that RNA synthesis increased exclusively in the hippocampus after 25 minutes of two-way avoidance conditioning. Bowman and Strobel (1969) found a similar increase following spatial maze discrimination tasks in rats. In follow-up studies, the question of whether inhibition of RNA synthesis by drug injection caused impaired learning was examined. Initial results (Nakajima, 1969) suggested that this was the case, but further research (Nakajima, 1973; Gattoni & Izquierdo, 1973) led to the conclusion that caution is necessary in attributing these results to RNA effects and not drug effects.

The recent work on long-term potentiation (LTP) (Bliss & Lomo, 1973; Bliss & Gardner-Medwin, 1973; Alger & Teyler, 1976; Douglas, 1977; McNaughton, Douglas, & Goddard, 1978) in hippocampal neurons may also apply to this learning hypothesis, although indirectly. These findings are particularly interesting in that long-term changes, like those which presumably must underly the process of learning, have been shown to occur in the hippocampus but have not been located elsewhere to nearly the same extent.

Two studies looking at conditioning-induced responses in hippocampal single units are also relevant. Hirsch (1973) used a latent inhibition paradigm and found that responses of single units in CA1, CA2, and CA3, most likely pyramidal cells, to the CS were established more slowly for groups which experienced long pre-conditioning sessions, a finding which parallels the behavioural evidence for normal animals. Thus the latent inhibition effect is found in single units within the hippocampus. A similar study was reported by Segal and Olds (1972), who looked at initial pseudo-conditioning of CA1, CA2, and CA3 units with two tones followed by subsequent food pellet conditioning to only one of the tones. During pseudo-conditioning few hippocampal units responded. During conditioning a conditioned response to the CS+ was established, while units showed no conditioning to the other tone. Finally Hirano, Best and Olds (1970) looked at unit responses of CA1 and CA3 pyramidal cells during novel stimulus habituation, discrimination conditioning, and extinction, and found no related unit responses during habituation, marked conditioning of unit responses during conditioning, and a response decline during extinction. Interestingly the final response level after extinction had been completed was higher than original baseline rates before conditioning, which suggests that the original associations remain in a latent form.

These three studies, along with the LTP and RNA evidence, clearly point to a learning role for the hippocampus, specifically one concerned with true conditioning, as opposed to pseudoconditioning. This is puzzling in light of the evidence cited earlier which implicates the hippocampus in a system dealing with non-reinforcing stimulation.

Memory Function Hypothesis

The evidence concerning hippocampal involvement in memory functions can most conveniently be divided into two main areas. Since a memory problem is inferred from an obtained result of impaired performance it is impossible to distinguish between underlying problems with consolidation (ie. the information no longer exists), or retrieval (ie. the information still exists but cannot be obtained from its place of storage). Thus the evidence to be reviewed applies to one or the other, or both of these alternatives within the broad rubric of memory function.

Some theta evidence is relevant at this point. Landfield, McGaugh, and Tusa (1972) found that the amount of theta correlated highly with the degree of retention of a passive avoidance task. Animals which showed good retention also showed high levels of theta during performance. As well, they showed the most theta suggesting that consolidation processes and hippocampal theta were related.

It is with the memory consolidation hypothesis that the human clinical evidence is most closely aligned. Scoville and Milner (1957) and Penfield and Milner (1958) reported that patients with hippocampal damage were incapable of retaining information past the span of their short-term memory. These findings led them to make two conclusions:

1. Consolidation or storage occurs in the hippocampus.
2. Consolidation of information strengthens over time, and the consolidation process is highly vulnerable to disruption immediately following learning.

It should be pointed out, however, that these conclusions are subject to serious criticism. As Izquierdo (1975) pointed out, the results upon which these conclusions were based were obtained from patients with lesions which were, first, not large enough to constitute true hippocampal ablation, and second, associated with other brain structures. These facts suggest, therefore, that to attribute these impairments of consolidation solely to damage of the hippocampus is not justified.

Subsequent studies, designed to test this proposal of time-dependent disruption of consolidation, have been conducted. Avis and Carlton (1968) and Hughes (1969) employed retrograde amnesia designs using hippocampal spreading depression as the disrupting agent. Both studies employed a design reported by Carlton and Vogel (1967) involving a conditioned emotional response (CER), and found that when hippocampal spreading depression was induced 24 hours after a learning trial and subjects were tested four days hence, amnesia resulted. Tests at 21 days following depression, though, demonstrated partial retention, suggesting that retrieval mechanisms, not consolidation problems, might be at fault. Further study, (Kapp, 1971) showed that rats given hippocampal spreading depression ten seconds after conditioning showed permanently impaired retention, indicating a consolidation problem. However rats given hippocampal spreading depression at 24 or 72 hours after learning were amnesic when tested four days later but showed recovery if tested 21 days later. Kapp (1971) interpreted these results as indicating that initial disruption of hippocampal activity immediately following learning, impaired consolidation processes, while disruption occurring at a longer post-learning interval caused only a temporary impairment of retrieval processes.

Finally, as mentioned previously, the pre-operation learning evidence also suggests a retrieval deficit, as opposed to one of consolidation, since learning has been given ample time to become consolidated in these experiments.

C. Spreading Depression As A Means Of Producing Reversible Lesions

One means of producing a reliable temporary disruption of the activity of the neurons within an area is to induce spreading depression (SD). This phenomenon was first reported by Leao (1944) who studied its occurrence in the cerebral cortex, as have most of the researchers who have subsequently studied the effect. (For excellent reviews of the phenomenon of SD see Marshall (1959) and Ochs (1962).) The presence of cortical SD (CSD) is manifested in a sequential depression of spontaneous EEG activity recorded from electrodes located at increasing distances from the site of SD initiation (Ochs, 1962; Leao, 1944). The typical rate of spread is quite slow, about two to six millimeters per minute. Stimulation can be achieved by a variety of agents; mechanical (Zachar & Zacharova, 1961), heat and ultrasonic radiation (Ueda, Bures, & Fisher, 1976), cooling (Zacharova & Zachar, 1961), electrical stimulation (Van Harreveld & Stamm, 1951; Marshall, 1959), and application of chemical agents including ammonium chloride and calcium chloride (Ochs, 1962), glutamine, asparagine, and aspartic acid (Van Harreveld, 1966; DoCarmo & Leao, 1972; Fifkova & Van Harreveld, 1974), and G-strophantine (Janebova, 1968). Typically though, most researchers use potassium chloride (KCl), either crystals or in solution, to elicit SD. After stimulation the EEG record diminishes in amplitude and remains depressed for a period which depends on the intensity and type of eliciting agent employed. In most cases this period is on the order of one half hour to one hour, although much longer durations have been reported (Leao, 1944; Van Harreveld & Stamm, 1951). Other changes accompanying SD include a drastic increase in tissue impedance (Van Harreveld & Ochs, 1957; Hoffman & Clark, 1973), marked vasodilation in the affected area (Leao, 1944b; Buresova, 1957), a significant swelling of the apical dendrites (Van Harreveld, 1958; Van Harreveld & Khattab, 1967), and inhibition of protein synthesis (Ruscak, 1964; Bennett & Edelman, 1969).

SD has been demonstrated in a number of different tissue areas, *in vivo* and *in vitro* alike. Subcortical structures in which it has been discovered include rat hippocampus (Weiss & Fifkova, 1960); rat caudate nucleus (Bures, Hartman, & Lukyanova, 1967), and catfish cerebellum (Nicholson & Craig, 1975). It has also been found in other areas such as the retina of various vertebrate species (Gouras, 1958; Van Harreveld & Fifkova, 1970; Ramos, 1975), and brain tissue cultures of neuronal and glial cells together and glial cells alone (Walker, 1972).

It should be mentioned that hippocampal SD (HSD) tends to reliably induce seizure-like, high-amplitude, synchronous spike discharge, either singly or in bursts, as well as periods of depressed hippocampal EEG activity (Grossman & Mountford, 1964; Kapp, 1971). Hence HSD is perhaps more properly referred to as non-specific hippocampal disruption in some cases, since depression and spike trains seem to be incompatible.

Although there has been a large amount of speculation on the physiological mechanism underlying SD, currently two major variants of the same theory are most commonly accepted. The basic hypothesis upon which these two variants are based is that the initial stimulus causes intense local neuronal activity which leads to the release of some cellular agent in large quantities. This agent then diffuses to neighbouring cells and excites them, causing them to fire in turn and release further amounts of this agent, thus continuing the cycle. The two variants differ only in the candidate which they propose for the released element.

In 1956 Grafstein proposed that potassium ions (K+) were the released substance, since K+ is known to be released by intense neuronal firing (Brinley, Kandel, & Marshall, 1960) and also known to have a depolarizing effect of its own. This hypothesis has received a large measure of supporting evidence from subsequent research, primarily concerned with measuring extracellular K+ levels during CSD. A large proportion of these experiments have confirmed that extracellular K+ levels rise during CSD (Prince, Lux, & Neher, 1973; Mayevsky, Zeuthen, & Chance, 1974; Higashida, Mitarai, & Watanabe, 1974; Sugaya, Takato, & Noda, 1975).

The second variant proposes glutamate as the diffusing agent. The chief proponent of the glutamate hypothesis is Van Harreveld (1959, 1966). The properties of glutamate, namely that it is a depolarizing transmitter, and can depolarize pre-synaptic and post-synaptic membranes alike (Freeman, 1976), provide support for the glutamate hypothesis. So does the fact that glutamate can reliably elicit SD (Van Harreveld, 1959; Trury & Feher, 1971; Ramos, 1975). Also glutamate has been shown to be released during SD (Van Harreveld & Kooiman, 1965; Van Harreveld & Fifkova, 1970). The resolution of these two hypotheses requires further research, but it is generally concluded that the mechanism involved is one of diffusion of a released depolarizing agent.

Elucidation of the underlying mechanism notwithstanding, SD provides quite an elegant means of producing a reversible lesion or ablation in the hippocampus. Recovery of the EEG record can be reliably demonstrated (Kapp, 1971). For this reason it is employed in the current experiment, since it affords two main advantages. The first is that it is temporary, allowing subjects to be depressed at certain times, yet normal at others. The second is that it allows recovery of impaired performance to be demonstrated within relatively short periods of time.

D. Statement Of The Problem

One can view the latent inhibition paradigm as consisting of three phases, a pre-conditioning, conditioning, and testing phase. Thus the difference between normal animals, which show latent inhibition, and lesioned animals, which do not, must lie in the fact that during one of these three phases an intact hippocampus is crucial for latent inhibition to occur. Of course it is also possible that an intact hippocampus must be present during two or even all three of these phases, but it is certain that during at least one phase an intact hippocampus is necessary.

Prior to this time, the majority of attempts to specify the role of the hippocampus have treated the learning-performance sequence as a unified process. For example, lesion studies involve an experimental manipulation prior to the learning-performance sequence, while consolidation disruption experiments look at processes which occur after learning. This experiment regarded the learning-performance sequence as three separate phases. The first two phases, the preconditioning and the conditioning phase, formed the learning element, while the last phase, the testing phase, formed the performance element. HSD was employed to produce reversible disruptions of hippocampal activity in different groups during different phases of the latent inhibition paradigm. The temporary nature of the disruption then allowed the groups to be run through subsequent phases with unimpaired hippocampal function. In this way the effect of a disrupted hippocampus during a single phase could be studied, since the hippocampus was normal during the remaining phase or phases.

One of the valuable consequences of this approach was that it allowed conclusions to be drawn regarding the need for an intact hippocampus to be present during learning or performance, or both, and hence, regarding the attention, learning, and response inhibition hypotheses of hippocampal function. For example if a normal latent inhibition result were obtained for subjects which had been given HSD during the preconditioning phase, it could be concluded that the hippocampus being intact is not a necessary condition for the subject to pay attention to the irrelevant preconditioning stimulus. Such a finding would seriously undermine the attention hypothesis. Similarly a finding that disrupting the hippocampus during testing had no effect on performance levels obtained from earlier tests without HSD would seriously undermine the response inhibition theory. Thus the experiment presented here was designed to discover when in the latent inhibition paradigm an intact hippocampus is most necessary to produce the normal result of latent inhibition.

E. Experimental Design And Resulting Predictions

The experiment to be described involved five groups. Two standard latent inhibition experiment groups, the first, a latent inhibition group (LI), which received pre-conditioning, and the second, a latent inhibition control (LIC), which did not, were run to ascertain whether the experiment was effective in producing the latent inhibition effect. In addition, three more groups were run. One (PSD) received HSD during the pre-conditioning phase in order to test the effect of a disrupted hippocampus during pre-conditioning. The second (LSD) received HSD during only the conditioning phase to test for the effect of a disrupted hippocampus during learning. The last group (PLSD) received HSD during pre-conditioning and conditioning alike. This group was included to emulate the lesion groups in the literature, to provide a control which would allow the conclusion that HSD and lesions were qualitatively similar. Table 1a provides a summary of the experimental design.

TABLE 1a. Summary of Experimental Design. This table provides a summary of the trials on which a given group or subgroup is exposed to HSD. Note that results for Test One are based on a group size of 8 subjects, since there is no difference between the subgroups on this test. However, Test Two and Test Three results are based on a group N of 4. A more elaborate description of this design is provided in the introduction, under Section E.

SYMBOLS :
- Trial consists of no tone and no HSD.
O Trial consists of tone but no HSD.
X Trial consists of tone and HSD.

TABLE 1b. Expected Pattern of Results According to the Attention, Learning, and Response Inhibition Hypotheses.
Note for the first two hypotheses no change is expected over the three tests, although the pattern for Test One is different between groups.

SYMBOLS :
L - Low Suppression Expected.
H - High Suppression Expected.

1a

	PRECOND	COND		TESTS		
				1	2	3
LI	0	0	N-	0	0	0
			SD-	0	X	0
LIC	-	0	N-	0	0	0
			SD-	0	X	0
PSD	X	0	N-	0	0	0
			SD-	0	X	0
LSD	0	X	N-	0	0	0
			SD-	0	X	0
PLSD	X	X	N-	0	0	0
			SD-	0	X	0

1b.

		HYPOTHESES								
		ATTENTION			LEARNING			RESP. INHIB.		
GROUPS	SUBGROUPS	1	2	3	1	2	3	1	2	3
LI	-N	L	L	L	L	L	L	L	L	L
	-SD	L	L	L	L	L	L	L	L	L
LIC	-N	H	H	H	H	H	H	H	H	H
	-SD	H	H	H	H	H	H	H	L	H
PSD	-N	H	H	H	L	L	L	L	L	L
	-SD	H	H	H	L	L	L	L	L	L
LSD	-N	L	L	L	L	L	L	L	L	L
	-SD	L	L	L	L	L	L	L	L	L
LSD	-N	H	H	H	L	L	L	L	L	L
	-SD	H	H	H	L	L	L	L	L	L

All groups, then, were allowed to perform during the first test without the influence of HSD. Following Test One, all groups were divided in half, and half were then subjected to HSD for Test Two. On Test Three the same conditions as Test One prevailed, that is, no subjects were under the influence of HSD. This part of the design allowed the study of the effects of a disrupted hippocampus during performance. If subjects, which demonstrated good performance on Test One, subsequently were impaired on Test Two under HSD, this would strongly suggest important hippocampal involvement during performance.

It can be seen that the groups described above allowed some specific predictions to be made. Group LIC was expected to show the highest level of performance on Test One. Group PLSD was also expected to show a high level of performance, since this group was expected to show results similar to lesion groups in the literature, ie. no latent inhibition. Group LI was expected to show a low level of performance on Test One, indicating that latent inhibition had occurred.

According to the various hypotheses of hippocampal function outlined above, different predictions could be made for the results for groups PSD, LSD, and PLSD. For each of these hypotheses, a different pattern of results for each group would be predicted. To clarify the application of these predictions, they were made on the assumption that each hypothesis would apply to only one phase of the experiment. Thus, for example, where the attention to irrelevant stimuli hypothesis is concerned, HSD given during the conditioning phase, in which the stimulus is no longer irrelevant, is assumed to have no effect. Similarly any HSD given before Test Two would be assumed to have no effect where the response inhibition hypothesis is concerned.

The attention hypothesis would predict that any group subjected to HSD during the preconditioning phase would be unable to properly monitor the irrelevant stimulus, hence they would be expected to show no latent inhibition, as if preconditioning had never occurred. Such an expectation applies to groups PSD and PLSD, while group LSD would be expected to exhibit latent inhibition, since attention to the irrelevant stimulus would be unimpaired for this group.

In contrast the learning hypothesis of hippocampal function would predict that any group given HSD during conditioning would be impaired in the CER conditioning and hence would exhibit little suppression of licking. HSD during preconditioning should then have no effect. Therefore the prediction is that groups LSD and PLSD would show little learning due to impaired CER conditioning, while PSD would also show little learning, presumably due to the occurrence of normal latent inhibition.

Lastly, the response inhibition hypothesis would predict that any administration of HSD prior to actual testing would have no effect on performance levels. Thus this hypothesis would predict that normal latent inhibition would occur on Test One for all groups except LIC, the latent inhibition control group. However, as far as Test Two is concerned, the hypothesis would predict that every subject which did show a high level of lick suppression on Test One, and was subsequently given HSD on Test Two, would show a dramatic impairment of lick suppression, which would recover when tested when the effects of HSD had worn off, on Test Three. Table 1b provides a summary of these predictions according to each hypothesis.

II. Method

A. Subjects

The subjects were 40 male albino rats, of the Sprague-Dawley strain, weighing approximately 450 grams when surgery began. The subjects were obtained from the University of Alberta Experimental Animal Colony at Ellerslie, Alberta, and were naive at the start of the experiment.

All subjects were housed individually on a 12 hour light dark cycle in a temperature controlled room adjacent to the room in which the experiment was performed. Subjects were permitted *ad libitum* food and water until the experiment began, at which time the water was removed from the home cages and was only available in a separate cage immediately after each trial. After the first six days water was also available in the testing chamber to allow the dependent measure of time taken to lick to be obtained.

Subjects were randomly divided into five groups of eight subjects after all had received identical hippocampal surgical implants. No subjects died prematurely during the experiment.

B. Apparatus

The training and testing apparatus consisted of two identical 11 inch square Plexiglas boxes, 11 inches wide, 11 inches deep, and 11 inches high with no ceilings. Each box contained a hinged section of the front wall, and a grid floor of stainless steel rods 1/4 inch in diameter placed one centimeter apart. The boxes also contained a hole for a removable drinking tube in the lower left wall. The lack of ceilings was to allow maximum movement of the cables and tubes, to which the subject was attatched.

Each Plexiglas box (testing box) was housed in a sound-attenuating chamber, 3 1/2 feet on a side, which opened from the front and contained a small one-way glass window inset in the door to allow observation of a subject during a trial. Each chamber was illuminated by a single 40 watt light bulb situated in the upper right front corner. Each chamber also contained a small loudspeaker in the upper right rear corner. The roof of each chamber contained a small hole to accommodate the EEG cable and injection tubes which were attatched to the subject.

All stimulus presentations and measurements of number of licks per trial and licking time were accomplished with electromechanical devices. The chamber loudspeakers were connected to timers and two Hewlett-Packard oscillators to allow a 1000 Hz tone with an intensity of 75 dB, measured inside the testing boxes, to be delivered at the appropriate time. The tone could be maintained for any length of time, although until the testing phase of the experiment all tone presentations were ten seconds long. A series of relays and a 16 mm film drive apparatus were employed to deliver the initial pre-conditioning stimulus at random intervals.

A lickometer consisting of a capacitance-operated switch connected via relays to mechanical counters was used obtain licking rate measurements.

A one milliampere footshock, one second in duration, was delivered via the grid floor of the testing box, using a constant-current shock generator of the type described by Bintz (1970).

A Beckman Type R Dynograph, equipped with four pens, one for each record, and a Grass AC Preamplifier (P511 Series), using a half-amplitude bandwidth of 10 Hz to 100 Hz, were employed to obtain cortical and hippocampal EEG records.

C. Training And Testing Procedures

Training involved conditioning a CER using a modified version of the procedures employed by Carlton and Vogel (1967).

Preconditioning - Days 1-6. Each day all subjects received a ten minute trial in the testing box. During these trials, all subjects, with the exception of group LIC, received ten presentations of the preconditioning stimulus which were non-reinforced. The presentations occurred at random intervals, so that a VI-1 min. schedule was achieved.

Thus only group LIC received no preconditioning, although it did receive identical treatment otherwise.

Water Tube Familiarization - Day 7-8. On days seven and eight drinking tubes were placed in the testing boxes and each subject was given one daily trial to familiarize itself with the drinking tube and to provide a baseline measurement of drinking rate. For each subject the time taken to make 110 licks at the tube was measured on both days. Times for the last ten licks were also taken separately. Thus the amount of time each subject spent in the testing box on each day was determined by the licking rate for that subject.

Conditioning - Day 9. On day nine each subject underwent one-trial CER conditioning in the test box. After an initial 30 seconds of licking at the drinking tube the tone was presented for ten seconds. At the completion of the tone a one milliampere footshock was delivered through the grid floor of the testing box. Following this the subject was removed.

Testing - Days 10-14. Days ten to 15 were the Test days. Each subject was tested once a day. Tests consisted of the following procedure. Each subject was placed in the testing box and allowed to lick at the drinking tube. After 100 licks had been completed the tone was presented and remained on until the subject had completed ten additional licks. The time taken to complete the ten licks was measured, up to a maximum of 300 seconds. If the ten licks had not been completed by 300 seconds the subject was removed from the testing box and the tone was turned off.

Water Training. For all subjects on all days, immediately following the daily trial in the testing box, the subject was removed from the testing box and given a ten minute period in a drinking cage with a water tube at the side to familiarize the subjects with drinking from the side of a cage, and also to provide daily water in a restricted time period. Following this each subject was then weighed and replaced in its home cage. Hence water was only available in the test box and/or drinking cage throughout the experiment.

HSD Schedule. An account of which groups received HSD during the experiment has already been provided (see Table 1), but will be briefly reviewed. During days one to six groups PSD and PLSD received HSD prior to and during the trial. On days seven and eight none of the groups received HSD. On day nine groups LSD and PLSD received HSD prior to and during the trial. On day 11, Test Two, half of each group received HSD. On day 14, Test Four, subgroup LIC with HSD received HSD prior to the test. Continuous EEG records of bilateral cortical and hippocampal activity were taken during any trial in which the subject was given HSD.

D. Preparation Of Electrodes

Cortical Electrodes

The cortical EEG electrodes were slot-head stainless steel screws with a diameter of one millimeter. An insulated lead was soldered, using stainless steel solder, to the side of the head of each screw, taking care to avoid introducing solder into the slot of the screw. The other end of the lead was soldered to the end of a female Amphenol pin which fit inside a plastic Amphenol plug strip. To avoid confusion during surgery, leads of different colours were used.

Hippocampal Outer Cannulae

The hippocampal outer cannulae, which also served to record hippocampal EEG activity, were constructed from 21 guage stainless steel tubing cut to lengths of approximately 20 millimeters. The ends were then smoothed and cleaned out to allow unobstructed insertion of the inner cannulae. An insulated lead was then soldered to the middle of each outer cannula barrel. The ends of the leads were then soldered to female Amphenol pins.

Insulation of each cannula was accomplished by slowly lowering it into Insulex insulating material to a depth of about ten millimeters, and then slowly removing it. Each cannula was then left to dry overnight. The next day the insulation was scraped from the tip to a distance of 1/2 millimeter with a scalpel. The insulation remaining was then tested for breaks by passing the barrel through a wire loop containing a film of saline solution which was connected to an ohmmeter. Deflections of the ohmmeter needle indicated a break in the insulation and the faulty barrel was then redipped and retested. Electrodes were then stored until just prior to surgery at which time they were placed in a bath of Savlon Germicidal solution.

Inner Cannulae

The inner cannulae were made from 27 guage stainless steel tubing, obtained from 27 guage stainless steel syringe needles which were 1 1/4 inches in length. 27 guage tubing fits snugly inside the 21 guage outer cannulae. The inner cannulae were cut to 25 millimeters and placed inside the outer cannulae so that they protruded 1/2 millimeter from the insulated end. The inner cannulae were then slightly bent to ensure that when inserted they would always extend 1/2 millimeter from the outer cannula tip.

E. Surgical Procedures

Following weighing subjects were anaesthetized with sodium pentobarbital (Diabutal) administered via intraperitoneal injection. When sufficiently anaesthetized they were placed in the stereotaxic instrument with the incisor bar adjusted at -3.0 mm. Next the scalp was shaved and swabbed with alcohol.

A midline incision, extending from approximately six millimeters anterior to bregma to the posterior crest of the occipital bone, was made and the skin was drawn back, exposing the skull, and clamped with hemostats. The periosteum was scraped away and the skull surface was dried. Following this bregma coordinates were taken and the skull was marked bilaterally over the site of the outer cannulae placement, which was situated 5.0 mm posterior to bregma and

5.0 mm lateral to the midline. In addition drill sites for the three cortical screw holes were marked. (Figure 1a provides a diagram of the electrode placements.)

The holes in the skull were produced using a hand-held Dremel drill with a drill bit 0.9 mm in diameter. Care was taken to avoid penetrating the dura during drilling. Following drilling the reference cortical electrode was first implanted followed by the two lateral cortical electrodes. Finally the first hippocampal outer cannula, which had been fixed in the stereotaxic electrode holder since the beginning of the operation, was slowly implanted to a depth of 4.5 mm and held rigid in the electrode holder. A small quantity of commercially available 5-minute epoxy glue was mixed and spread around the dried skull and cannula barrel. This was done to anchor the electrode firmly and to avoid the problem of the dental acrylic solvent dissolving the cannula insulation. When the epoxy was set, the electrode was then fixed in place using the standard method of coating it with layers of dental acrylic. The cannula was released from the holder when the dental acrylic was set (about 10-15 minutes). The remaining outer cannula was then placed in the vacant electrode holder and implanted using identical techniques.

Following implantation each electrode lead was inserted into the appropriate hole in the Amphenol plug strip, which had been cut in five hole strips with each hole colour-coded to match the lead colours. The plug was then centered along

Figure 1a. Diagram of Exposed Rat Skull Showing Implantation Site of Hippocampal Outer Cannulae and Cortical Electrodes. Hippocampal outer cannulae coordinates: 5.0 mm posterior to bregma, + or - 5.0 mm lateral to the midline, and 4.5 mm vertical. Cortical electrode coordinates: 2.0 mm posterior to bregma, 2.0 mm lateral to the midline.
The reference electrodes was implanted between the eyes, approximately 8-10 mm anterior to bregma.

Figure 1b. Diagram Showing Cross-Section of Cannulae Arrangement Illustrating the Polythene Tube Leading to the 10 Microlitre Syringe.
This figure also shows the outer cannula lead and the layers of epoxy cement and dental acrylic.

1a

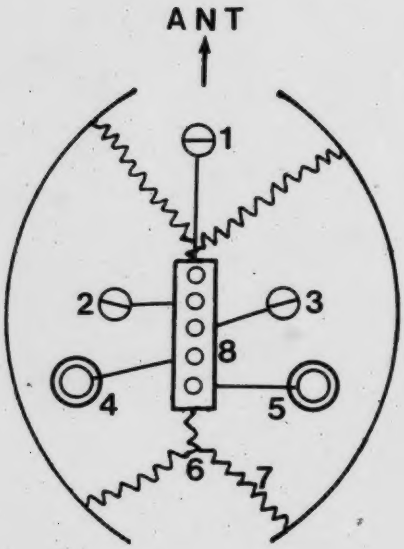


FIGURE LEGEND

1. CORTICAL REFERENCE ELECTRODE
2. LEFT CORTICAL ELECTRODE
3. RIGHT CORTICAL ELECTRODE
4. LEFT HIPPOCAMPAL CANNULA
5. RIGHT HIPPOCAMPAL CANNULA
6. LAMBDA
7. SKULL SUTURE LINES
8. 5-PIN HEAD PLUG ASSEMBLY

1b

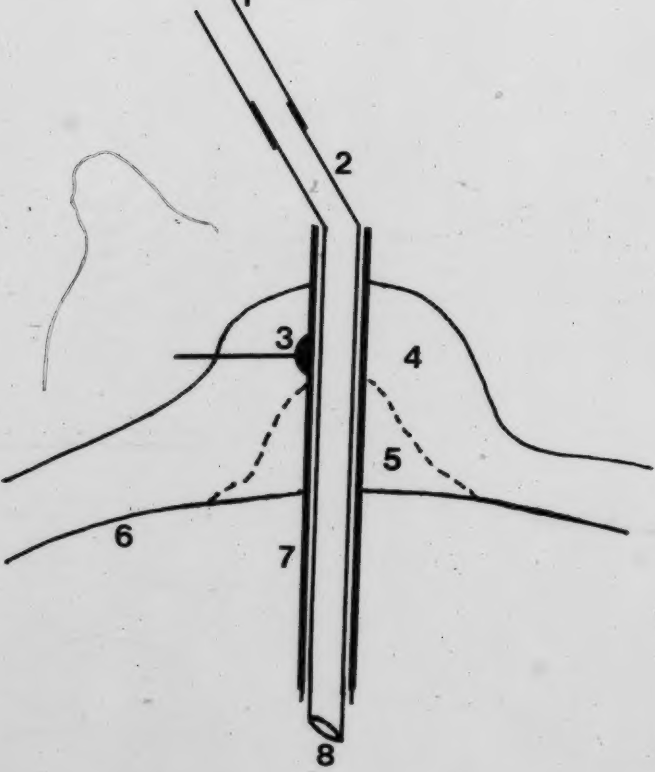


FIGURE LEGEND

1. POLYTHENE TUBING
2. 27 GUAGE INNER CANNULA
3. SOLDER JOINT AND OUTER CANNULA LEAD WIRE
4. DENTAL ACRYLIC CAP
5. EPOXY CEMENT LAYER
6. SURFACE OF SKULL
7. INSULATED 22 GUAGE OUTER CANNULA
8. PROTRUDING TIP OF INNER CANNULA

the midline of the skull and anchored with dental acrylic. When the acrylic was set two or three interrupted stitches, using 3-0 or 4-0 silk, were placed at either end of the incision, thus ensuring that the skin closed snugly around the dental acrylic headplug. Finally the wound edges were swabbed with Neosporin antibiotic ointment.

The subjects were then removed from the stereotaxic and attatched to the EEG cable to ensure that all electrodes were functioning properly. Subjects were then replaced in their home cages and allowed three or four days to recover from the operation.

F. Initiation Of HSD

HSD was produced by injecting a precisely controlled amount of KCl solution (conc. 25% by weight) into the hippocampus via the inner cannula while the subject was in the testing box.

Two ten microlitre syringes, one for each cannula, were attatched to polythene tubes which were in turn attatched to the bent end of the inner cannula. The polythene tubing fit snugly over the inner cannula and the syringe needle so that an airtight and watertight seal was achieved. The polythene tubes were approximately five to six feet in length to allow a maximum of movement. The tube and syringe were filled with KCl solution immediately prior to each trial.

After the subject had been introduced to the testing box and attatched to the EEG cable via the headplug, a baseline record consisting of activity in both cortices and hippocampi was obtained. Following this the inner cannulae were gently inserted, one at a time, into the outer cannulae to the full extent. (Figure 1b illustrates the cannulae arrangement.) This usually appeared as an artifact in the hippocampal EEG record. Following this, enough KCl solution (range 0.2 to 1.8 microlitres per trial) to produce a visible disruption of hippocampal activity was slowly injected into each hippocampus. More KCl was injected during the trial if signs of recovery occurred. This resulted in a guarantee that the HSD lasted throughout the trial, although precise measurements of the absolute duration of HSD after the trial were not possible, given the trial schedule. Pilot work completed previous to the experiment showed that the HSD lasted from two to six hours, although no subjects showed altered baselines when tested 24 hours later. At the end of the trial both tubes and the cable were removed and the subject was removed from the testing box.

III. Results

A. Histological Results

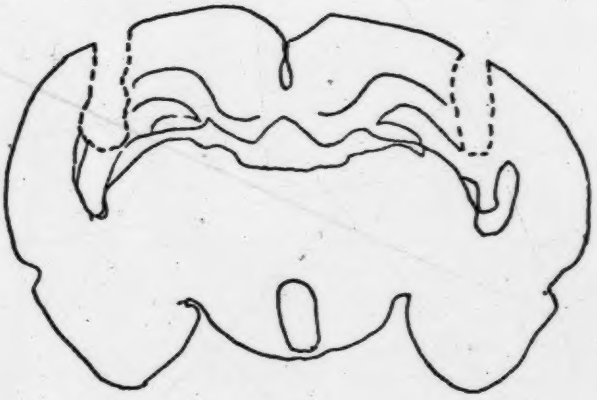
Following completion of the experiment all 40 subjects were deeply anaesthetized with Diabutal and perfused through the heart with a saline solution followed by a 10% buffered formalin solution. The brains were then removed and standard histological fixing, embedding, sectioning, and staining procedures were employed. Serial frontal sections, each 20 microns thick, were taken through the cannula implant area of each brain. Every tenth section was then mounted and stained using a Cresyl violet stain. Outlines of sections containing the maximum extent of damage to each side were then sketched, and electrode tip placements were checked for all subjects.

All of the electrode placements were verified to be in either the dorso-lateral or superior ventro-lateral hippocampus. In no case was a tip placement located in the diencephalon. Figures 2-6 present some representative section reconstructions for each group. These figures illustrate the damage produced by the cannula tract, and the location of the electrode tip (area outlined with broken line). The broken line in all diagrams also encompasses an area of gliosis at the tip of each cannula.

In addition to the usual extent of cannula tract damage, sections were also found with damaged areas displaced from the immediate tip of the electrode, most

Figure 2. Reconstructions of Maximum Bilateral Cannulae-Induced Lesions for 3 Subjects in Group LI.
Cannulae tracts are outlined in broken lines. Note that the tip of the tract is inside the hippocampus in all cases.

L1



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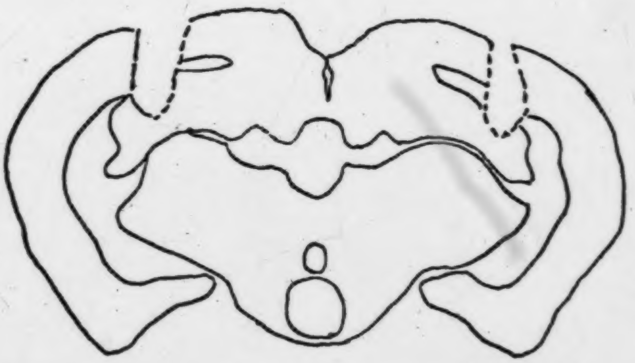

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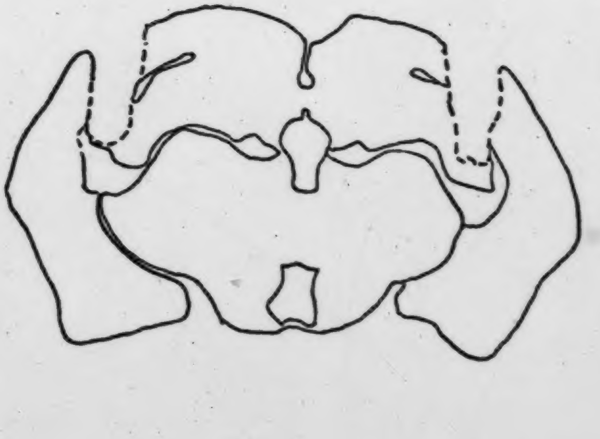
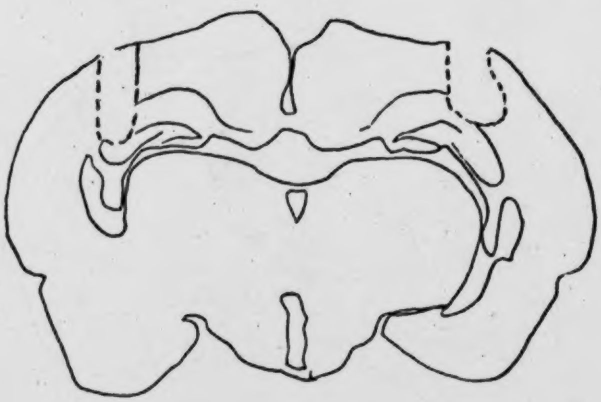


3

Figure 3. Reconstructions of Maximum Bilateral Cannulae-Induced Lesions for 3 Subjects in Group LIC.
Cannulae tracts are outlined in broken lines. Note that the tip of the tract is inside the hippocampus in all cases.

LIC



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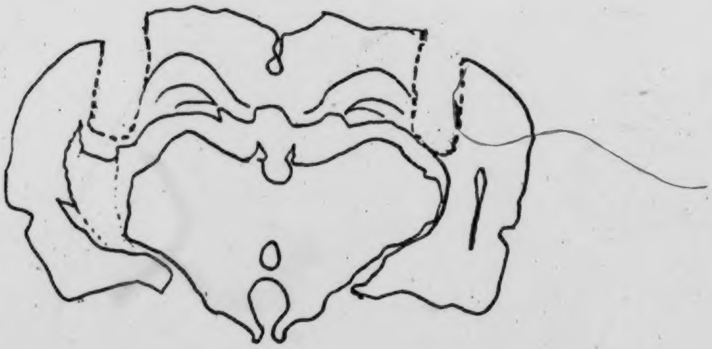

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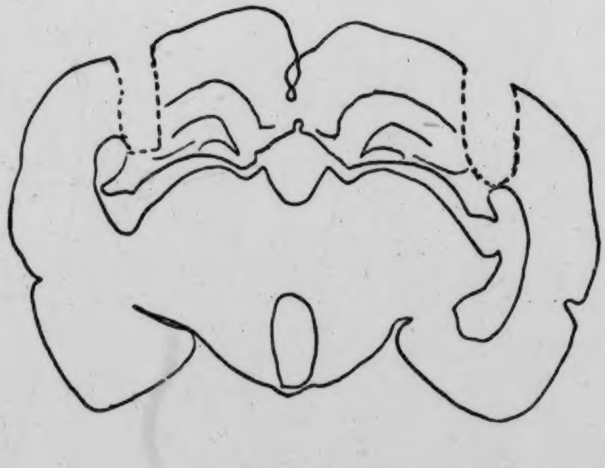
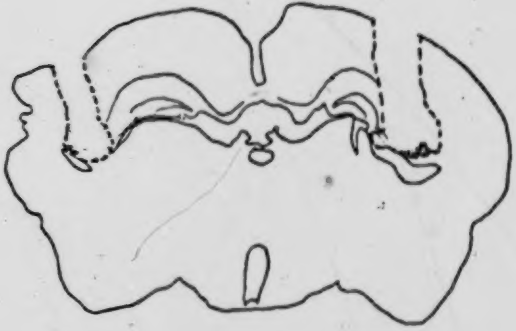


2

Figure 4. Reconstructions of Maximum Bilateral Cannulae-Induced Lesions in 3 Subjects in Group PSD.
Cannulae tracts are outlined in broken lines. Note that the tip of the tract is inside the hippocampus in all cases. Also note some irregularly shaped damage around the tip (particulary in subjects 4 and 5), possibly infection-induced.

PSD



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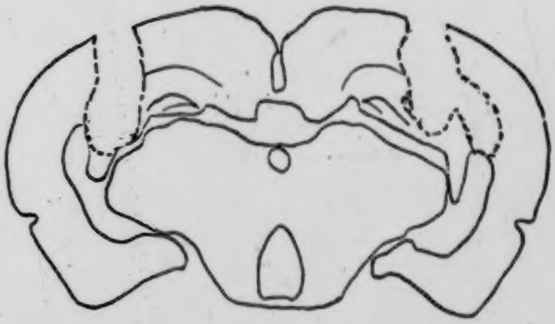
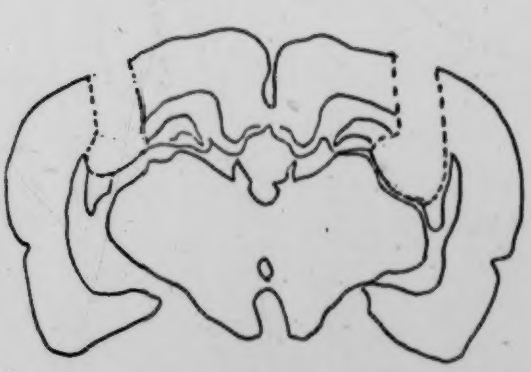


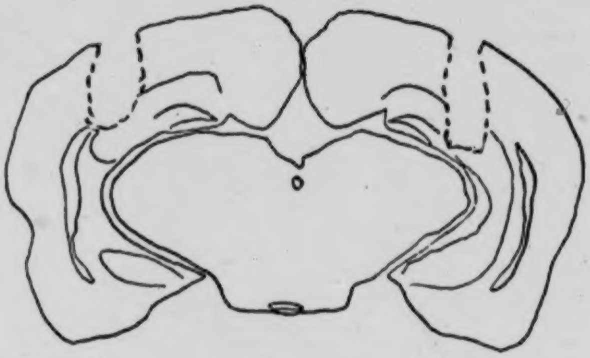
5



4

Figure 5. Reconstructions of Maximum Bilateral Cannulae-Induced Lesions in 3 Subjects in Group LSD.
Cannulae tracts are outlined in broken lines. Note that the tip of the tract is inside the hippocampus in all cases.

L S D



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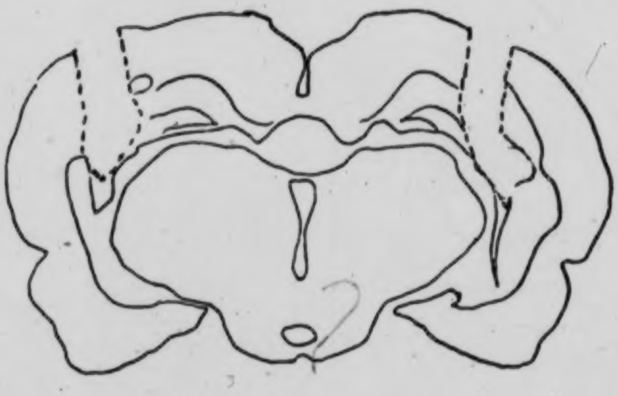

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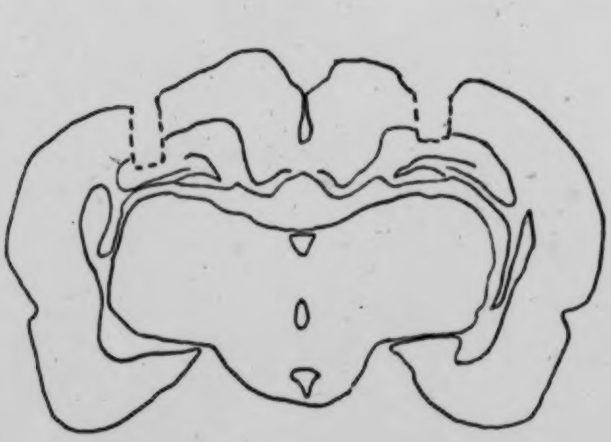
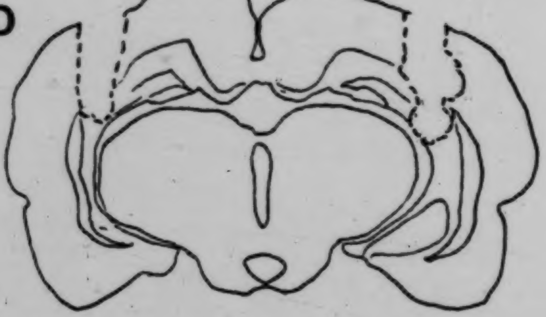


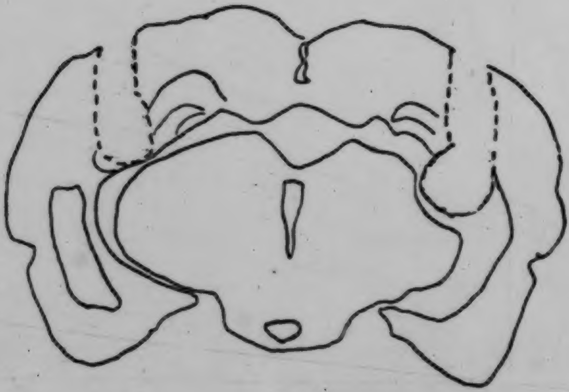
4

Figure 6. Reconstructions of Maximum Bilateral Cannulae-Induced Lesions in 3 Subjects in Group PLSD.
Cannulae tracts are outlined in broken lines. Note the the tip of the tract is inside the hippocampus in all cases. Also note the irregularly shaped damage, possibly infection induced, in subjects 2 and 5.

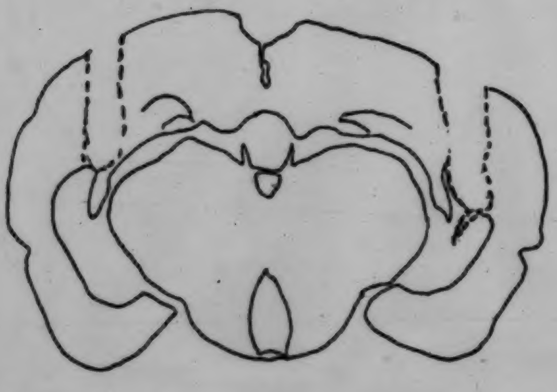
PLSD



5



2



1

likely due to the presence of infection, or possibly to the effects of the KCl solution. Examples of these sections showing infection-induced damage are given in Figure 7. It can be seen from this figure that in some cases the damage is well away from the electrode tip and also is not symmetrical, suggesting that it was not caused by an agent diffusing from the cannula.

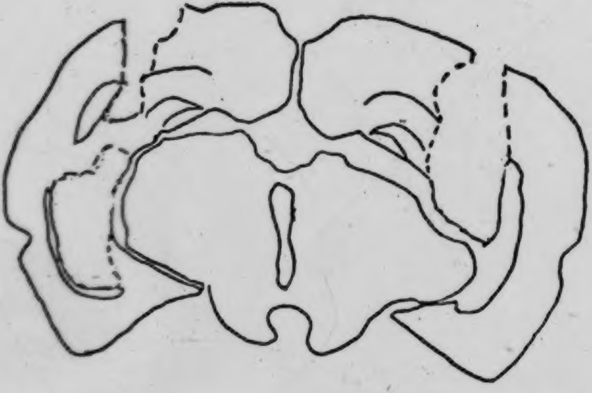
B. Electrophysiological Results

Baseline EEG Records

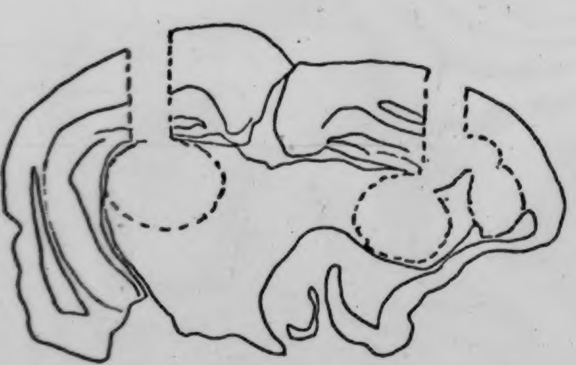
Examples of various baseline and KCl-injected EEG records are presented in Figures 8 through 19 presented below. For the purposes of clarity, all figures are presented together. It should be noted that Figures 8 to 15 are organized in pairs, such that the first figure is a baseline record, while the second is the corresponding record obtained after the introduction of KCl for that trial. The remaining figures, Figures 16 to 19, are further examples of KCl-injected records which show particular characteristics of HSD.

Figures 8, 10, 12, 14, and 16, present some representative baseline EEG records for all four channels taken on different experimental days. Baseline hippocampal records were characterized by relatively low frequency waves, in the three to six Hz range, of medium amplitude (see Figures 8, 10, 12). Other baselines showed slightly faster activity, as Figure 14 illustrates. Although there

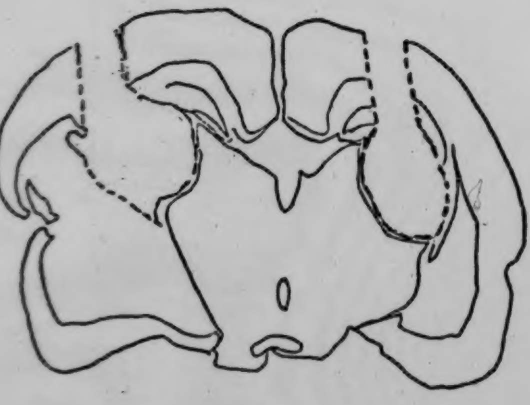
Figure 7. Reconstruction of Maximum Bilateral Cannulae Induced Lesions in Subjects Which Exhibited Massive Infection-Induced Damage.
Damage and cannulae tracts are outlined in broken lines. Note that in subject PLSD-3 the entire left dorsal and ventral hippocampus is destroyed. In subject LSD-1 massive bilateral damage inside the diencephalon has occurred, while in subject PSD-5 the lesioned area is the hippocampus. In fact the entire ventral hippocampus is non-existent, and no tissue was present at the time of perfusion. Note also the distortion of the diencephalon in this subject, caused by the large areas of damage immediately beside it.



PLSD$_3$



LSD$_1$



PSD$_5$

Figure 8. 4-Channel Baseline EEG Records for Subject PLSD-1 on Trial 3.
Note that hippocampal records show waves of larger amplitude. Note also that frequent bursts of theta (3-6 Hz) occur in the hippocampal records, and that cortical and hippocampal frequencies are similar.
LC - Left Cortex, LH - Left Hippocampus
RC - Right Cortex, RH - Right Hippocampus
Calibration: 1 sec and 200 microvolts.

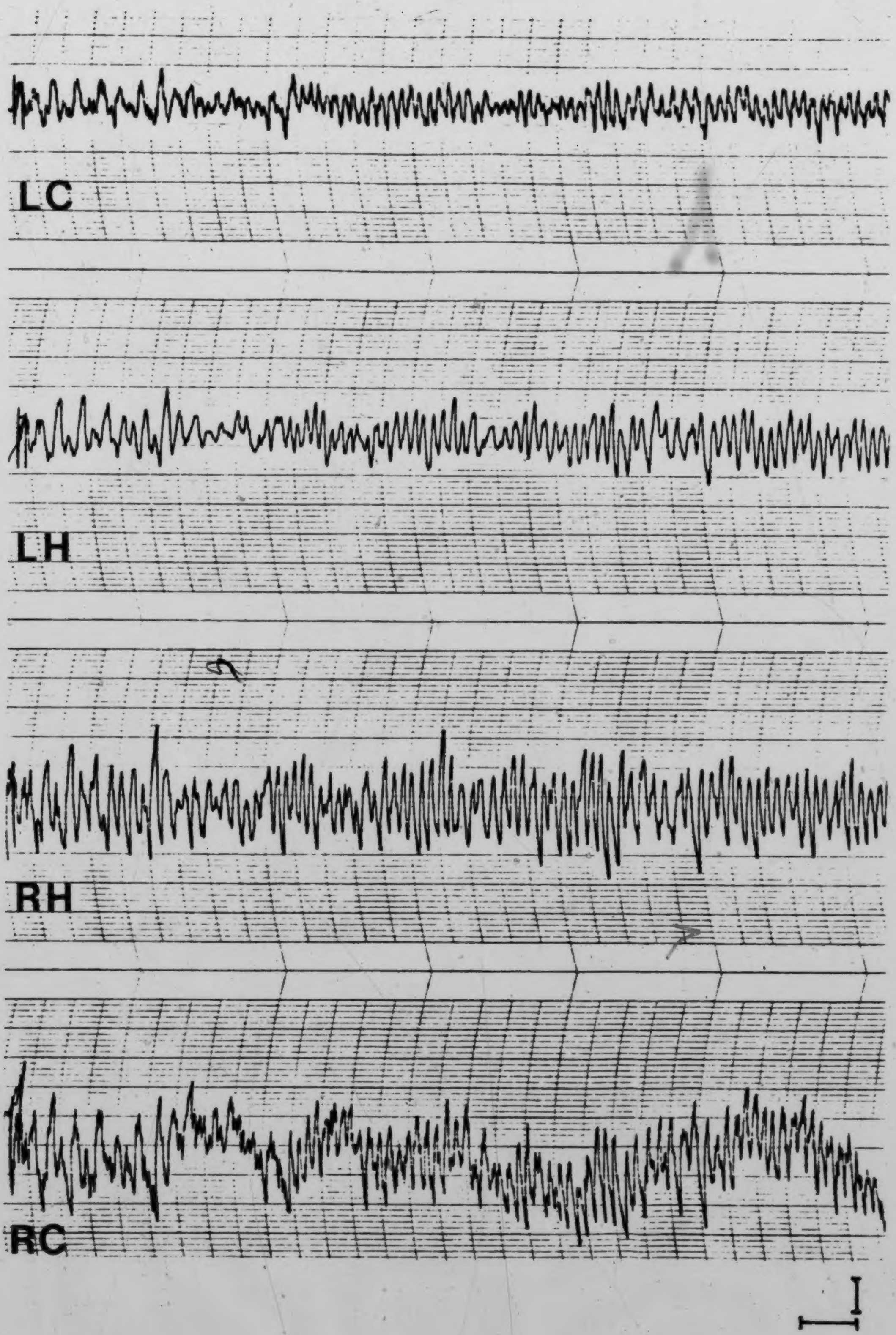
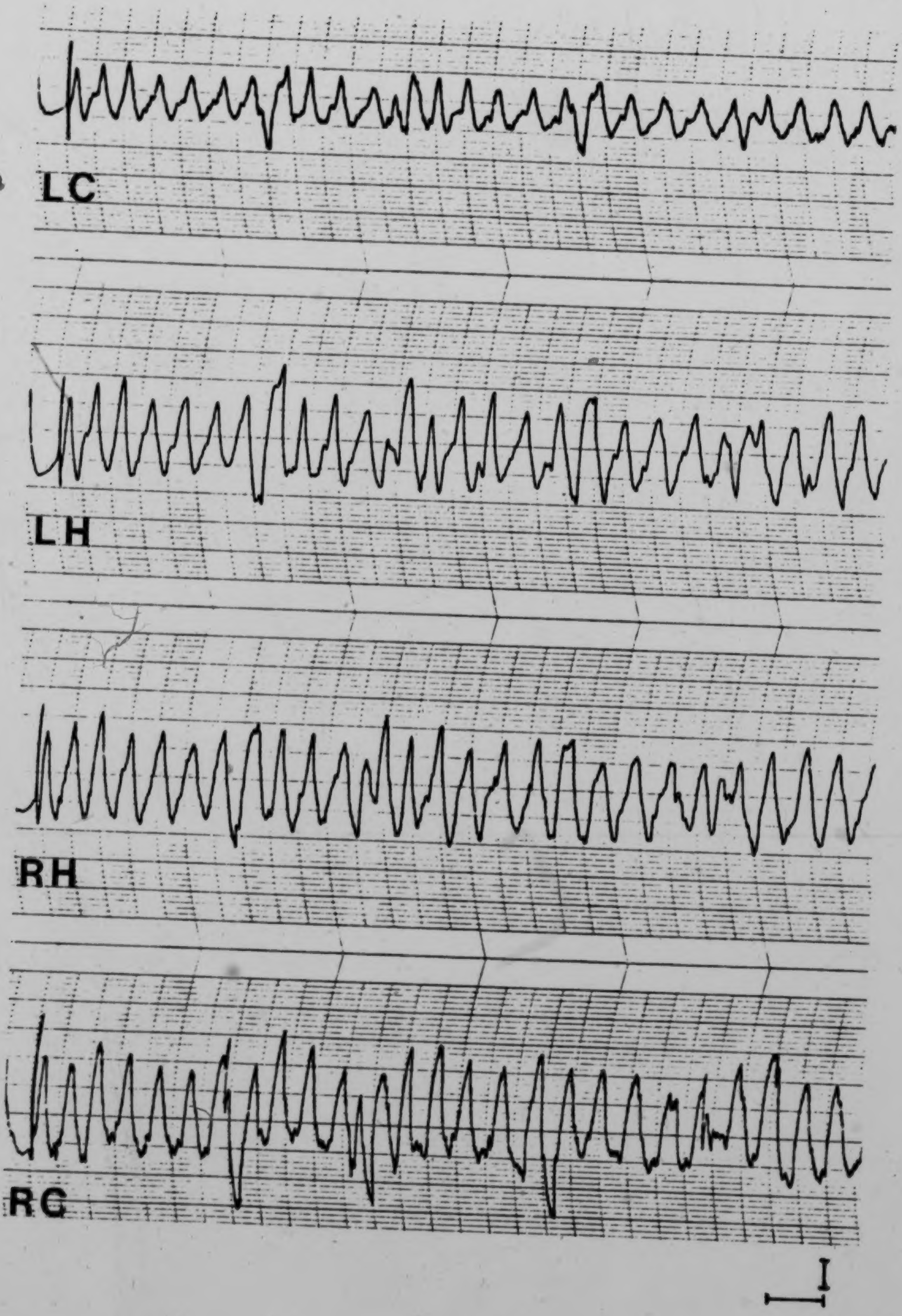

LC
LH
RH
RC

Figure 9. 4-Channel KCl-Injected EEG Records for Subject PLSD-1 on Trial 3: Example of decreased frequency.
Record obtained after bilateral injection of 1.0 microlitre of KCl. Compare with Figure 8 to see marked decrease in frequency following KCl injection. Note cortical following of hippocampal frequency.
LC - Left Cortex, LH - Left Hippocampus
RC - Right Cortex, RH - Right Hippocampus
Calibration: 1 sec and 200 microvolts.



LC
LH
RH
RC

Figure 10. 4-Channel Baseline EEG for
Subject PLSD-2 on Trial 6.
Note similarity of this record with Figures 8 and 12. Record shows bursts of hippocampal theta with following in the cortex.
LC - Left Cortex, LH - Left Hippocampus
RC - Right Cortex, RH - Right Hippocampus
Calibration: 1 sec and 200 microvolts.

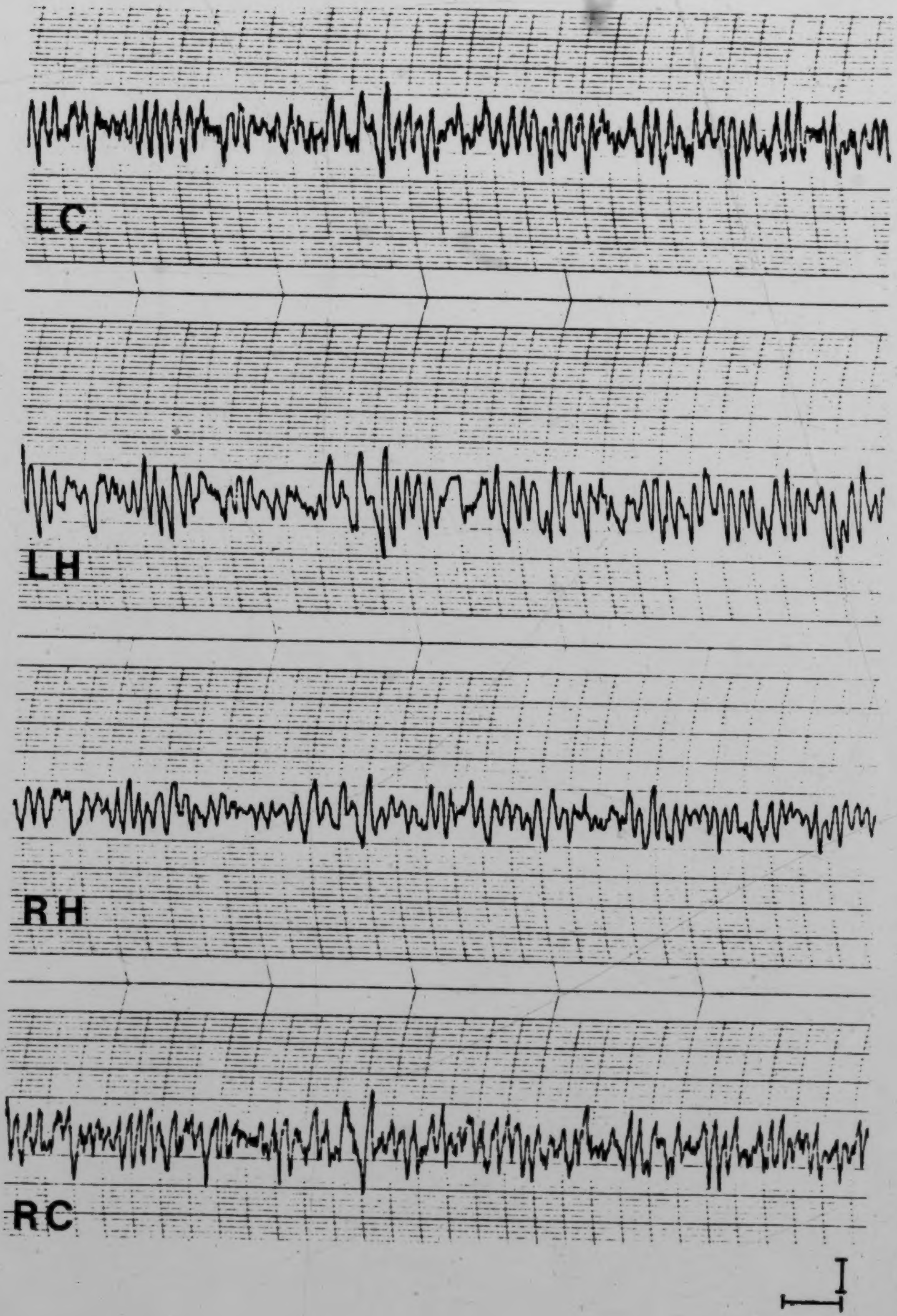

LC
LH
RH
RC

Figure 11. 4-Channel KCl-Injected EEG for Subject PLSD-2 on Trial 6: Example of spiking in only one hippocampus, as well as 4-channel decreased frequency.
Record obtained 1 minute following bilateral injection of 0.3 microlitres of KCl. Note the frequency similarities with Figure 9, and also the presence of spikes in only one hippocampus.
LC - Left Cortex, LH - Left Hippocampus
RC - Right Cortex, RH - Right Hippocampus
Calibration: 1 sec and 200 microvolts.

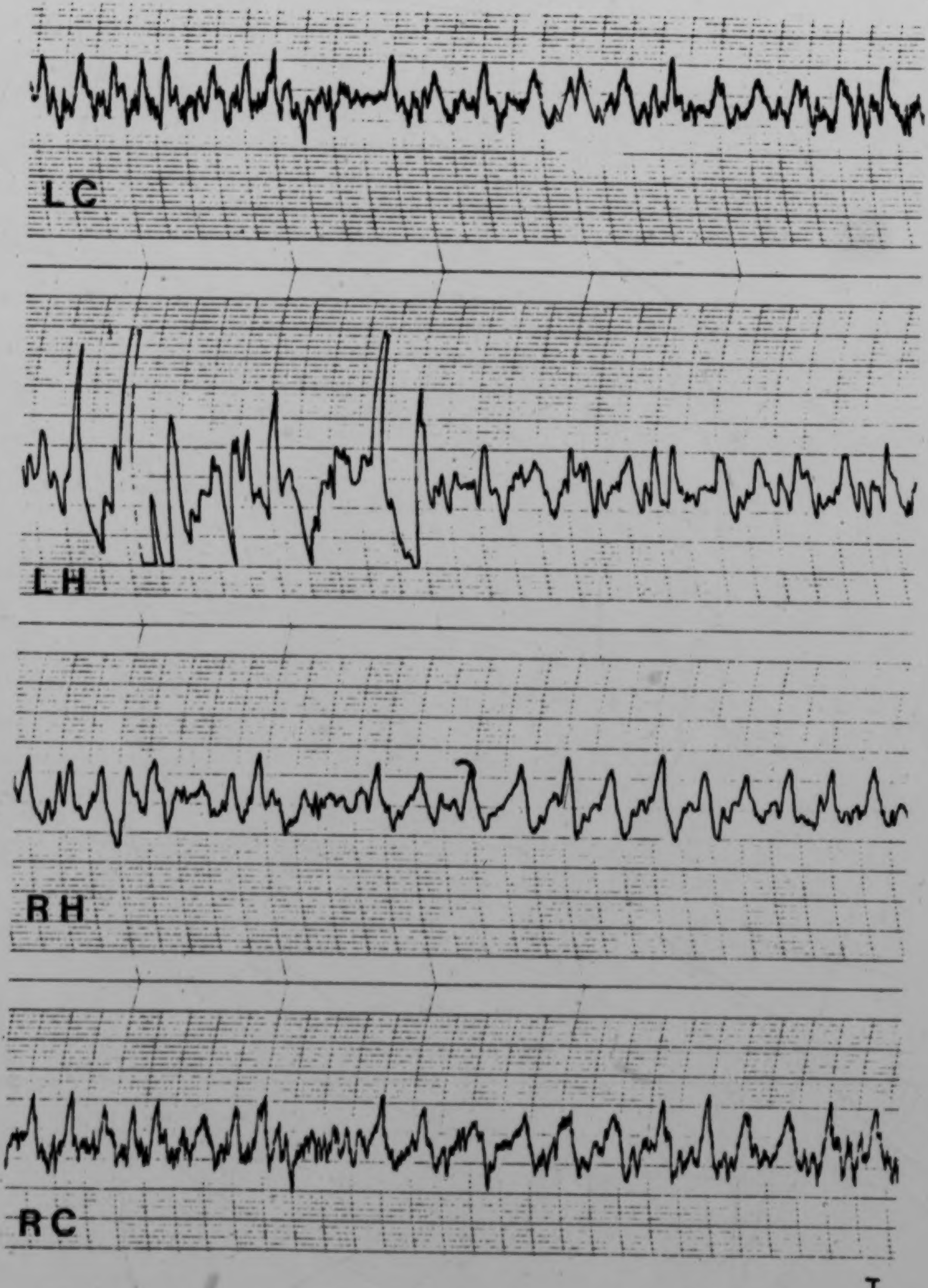

LC
LH
RH
RC

Figure 12. 4-Channel Baseline EEG for Subject PLSD-6 on Trial 3.
Note overall theta bursts, with some fast activity superimposed on theta waves. Also frequencies are similar for hippocampi and cortices.
LC - Left Cortex, LH - Left Hippocampus
RC - Right Cortex, RH - Right Hippocampus
Calibration: 1 sec and 200 microvolts.

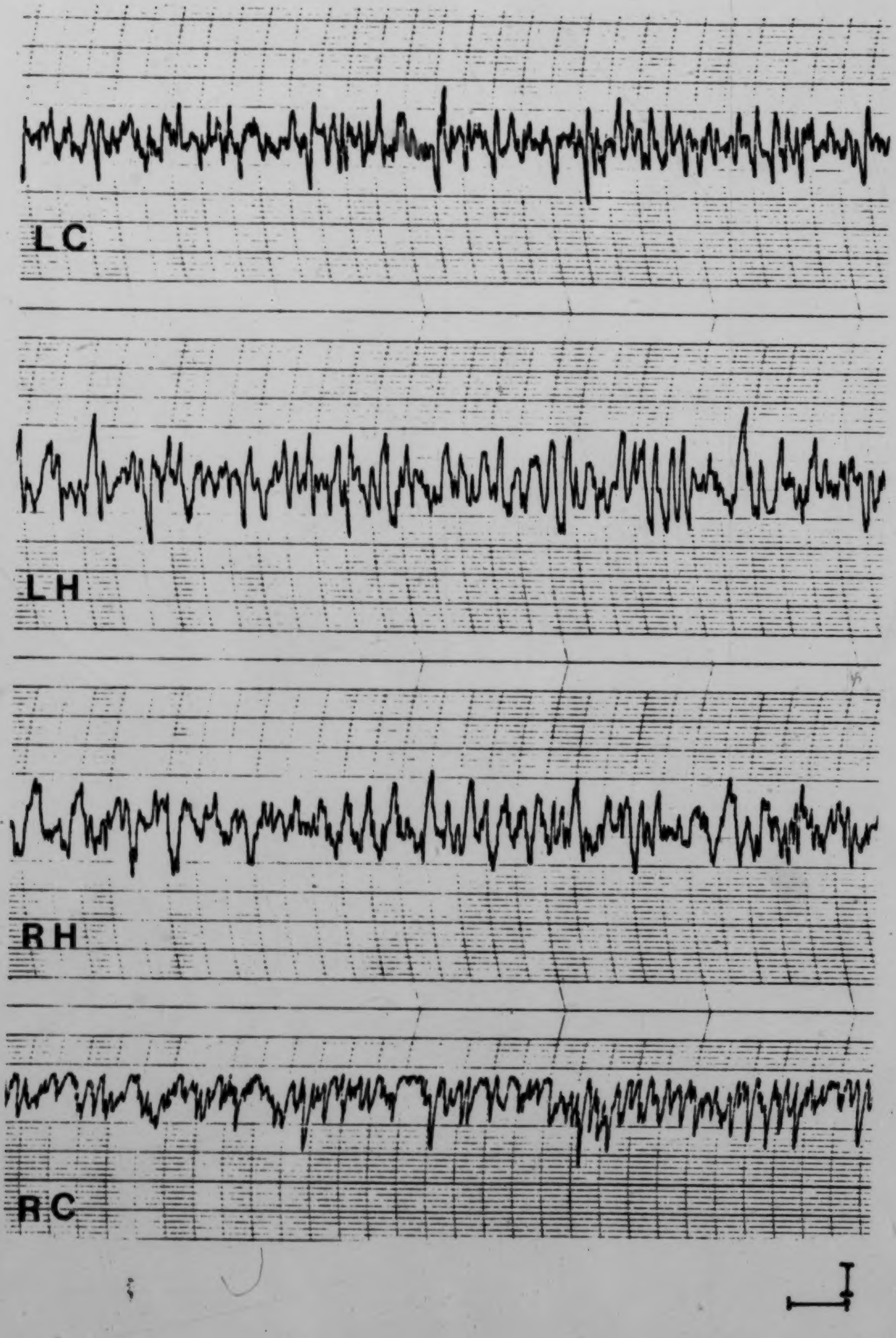

LC
LH
RH
RC

Figure 13. 4-Channel KCl-Injected Record for Subject PLSD-6 on Trial 3.
Record obtained 20 seconds following bilateral injection of 0.3 microlitres of KCl. Note dramatic 4 channel EEG depression, as compared with Figure 12.
LC - Left Cortex, LH - Left Hippocampus
RC - Right Cortex, RH - Right Hippocampus
Calibration: 1 sec and 200 microvolts.

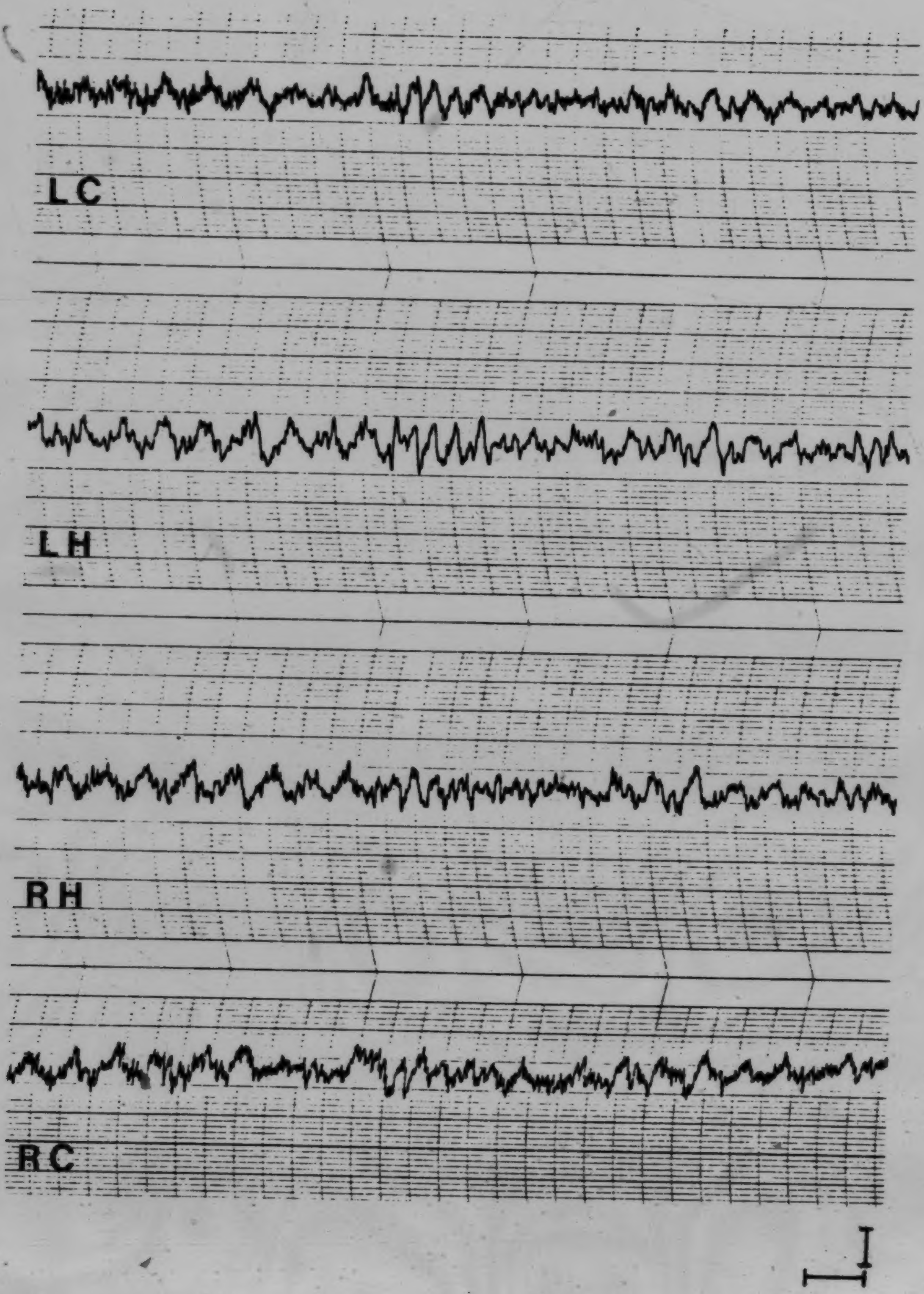

LC
LH
RH
RC

Figure 14. 4-Channel Baseline EEG Record for Subject LSD-4 on Trial 7 (Shock Trial). Note high amplitude hippocampal activity in theta range. Cortical activity shows more desynchrony.
LC - Left Cortex, LH - Left Hippocampus
RC - Right Cortex, RH - Right Hippocampus
Calibration: 1 sec and 200 microvolts.

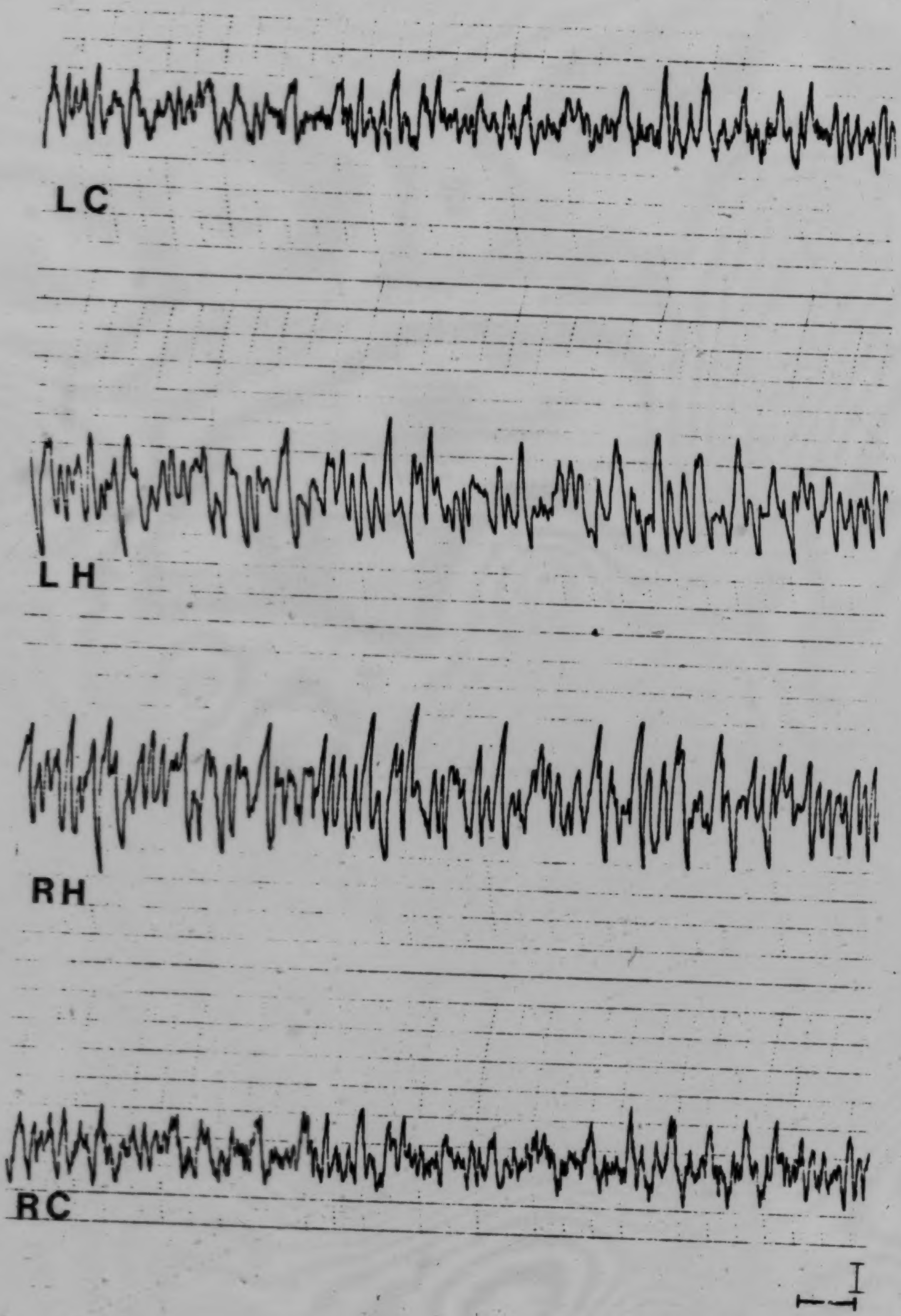

LC
LH
RH
RC

Figure 15. 4-Channel KCl-Injected EEG for Subject LSD-4 on Trial 7: Example of 4-Channel spiking.
Record obtained immediately after footshock following bilateral injection of 0.9 microlitres of KCl. Note violent spiking, particularly in the RH, and cortical spiking. Also note high frequency of the spike trains. Record provides good evidence of hippocampal disruption immediately following footshock during the conditioning trial.
LC - Left Cortex, LH - Left Hippocampus
RC - Right Cortex, RH - Right Hippocampus
Calibration: 1 sec and 200 microvolts.

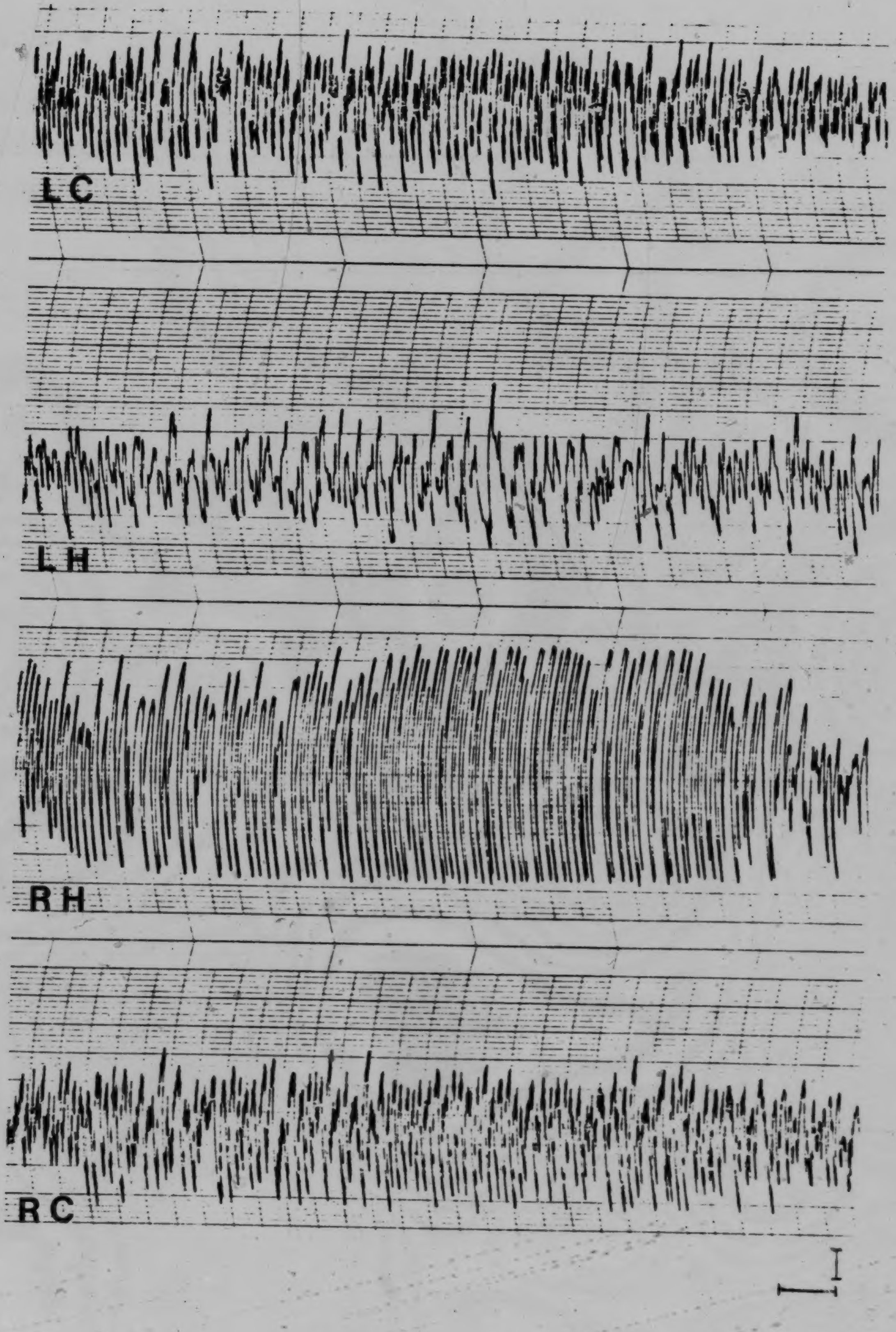

LC
LH
RH
RC

Figure 16. Comparison of Baseline and KCl-Injected Hippocampal EEG Records for Subject PSD-1 during Test Two: Example of classic HSD.
Top two traces are baseline hippocampal EEG records showing high amplitude waves, with some theta bursts.
Bottom two traces are KCl-injected hippocampal records obtained 150 seconds after bilateral injection of 0.3 microlitres of KCl. Note dramatic prolonged depression in both channels, with infrequent low amplitude spikes.
LH - Left Hippocampus
RH - Right Hippocampus
Calibration: 1 sec and 200 microvolts.

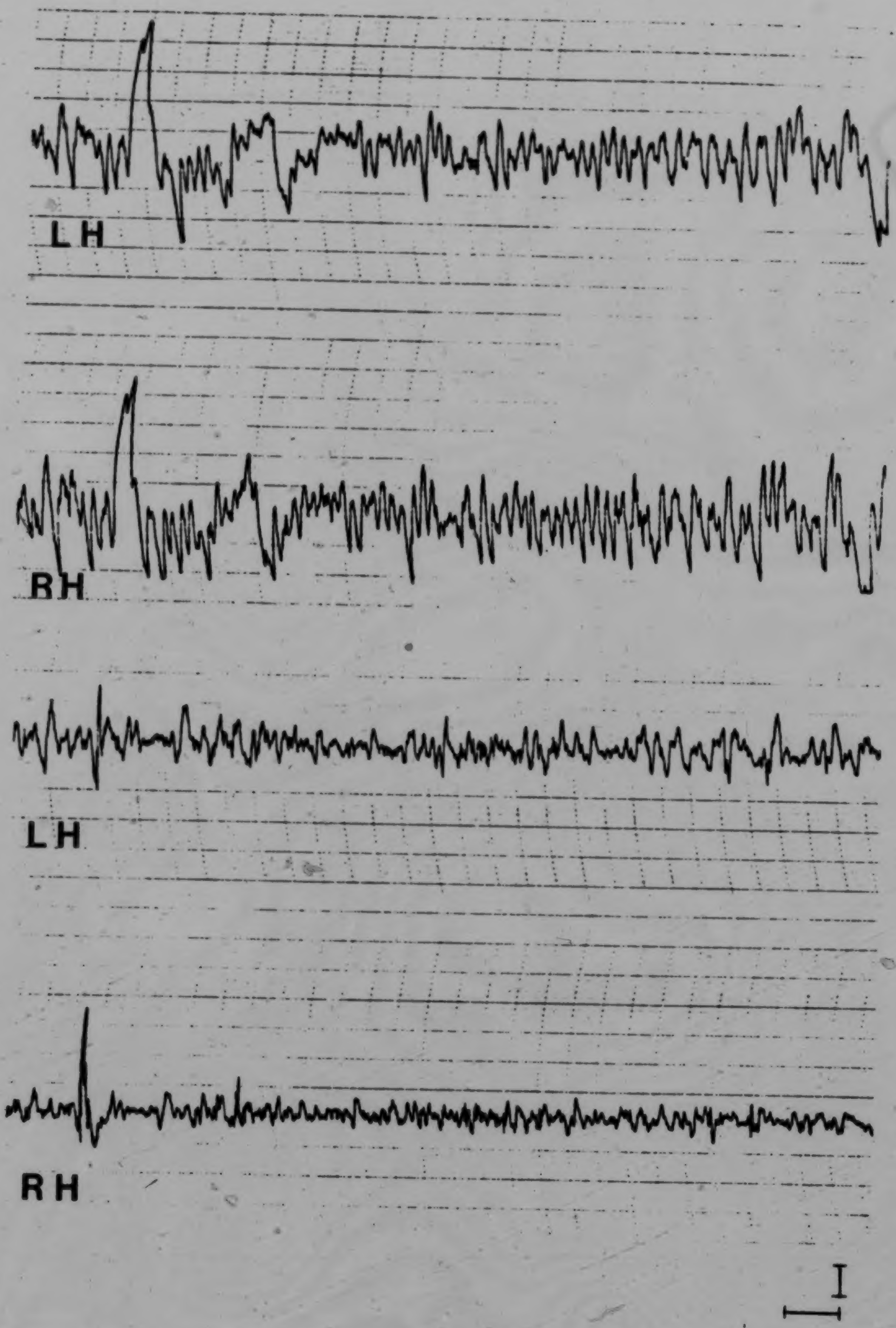

LH
RH
LH
RH

Figure 17. KCl-Injected Hippocampal EEG Showing Depression in One Trace and Spiking in the Other.
Record obtained from subject PLSD-1 after bilateral injection of 0.5 microlitres of KCl. Note that spiking activity in the RH is not seen in the LH, which shows consistent depression.
LH - Left Hippocampus
RH - Right Hippocampus
Calibration: 1 sec and 200 microvolts.

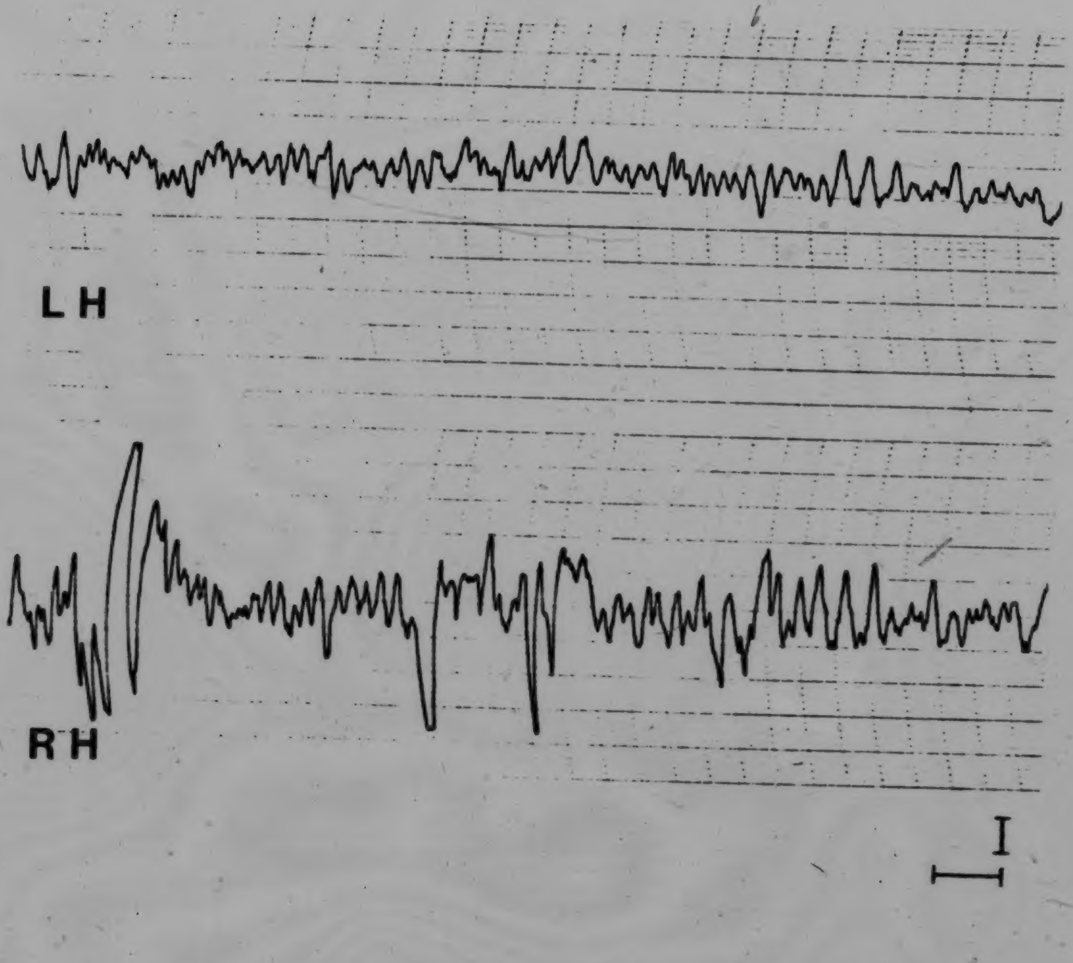

L H
R H

Figure 18. 4-Channel KCl-Injected EEG Record for Subject PSD-3 on Trial 5: Example of 4-channel spiking.
Record obtained after bilateral injection of 0.5 microlitres of KCl. Note that although all traces show spiking activity, the cortical records are not as consistent and do not follow all hippocampal spiking.
LC - Left Cortex, LH - Left Hippocampus
RC - Right Cortex, RH - Right Hippocampus
Calibration: 1 sec and 200 microvolts.

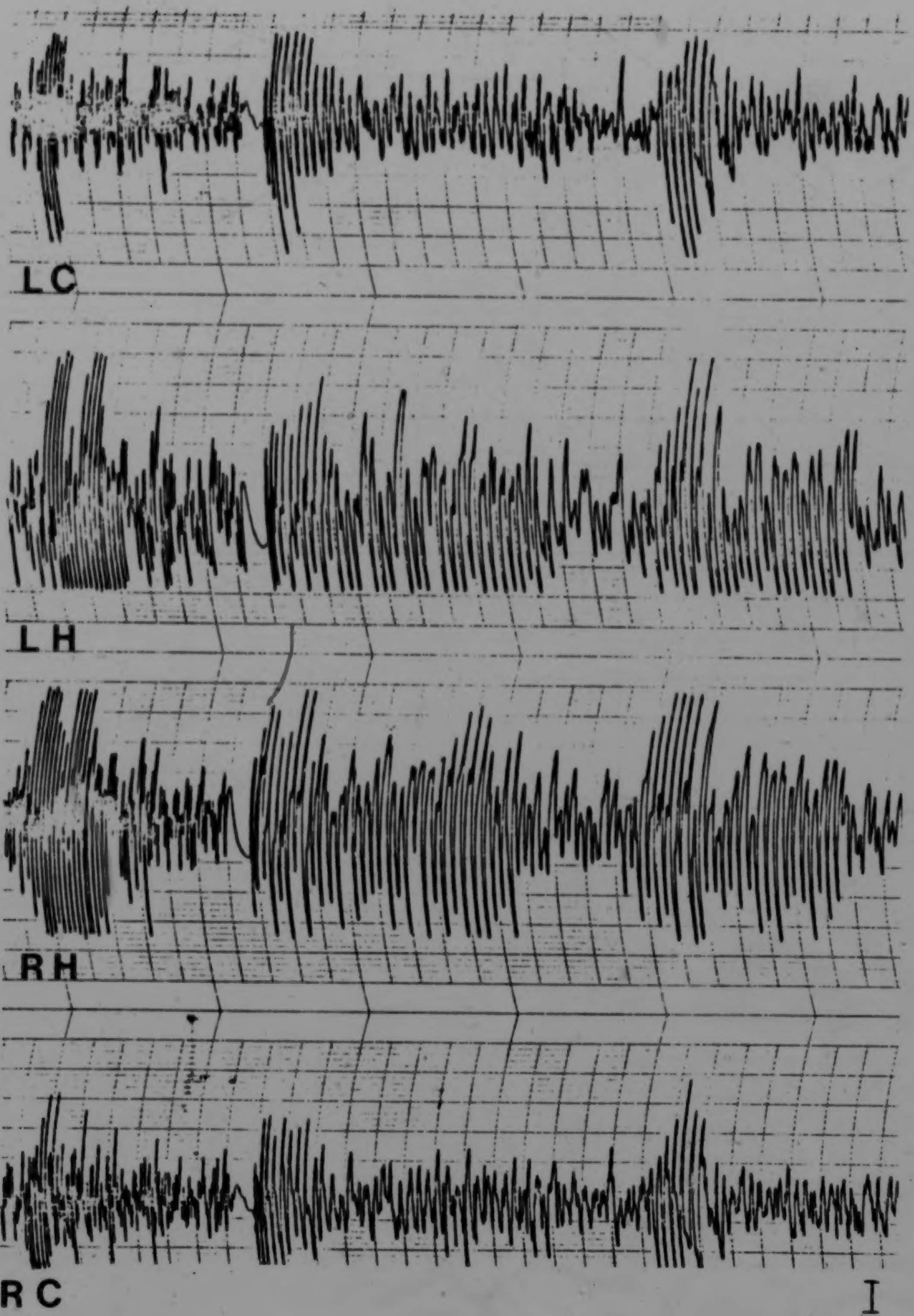
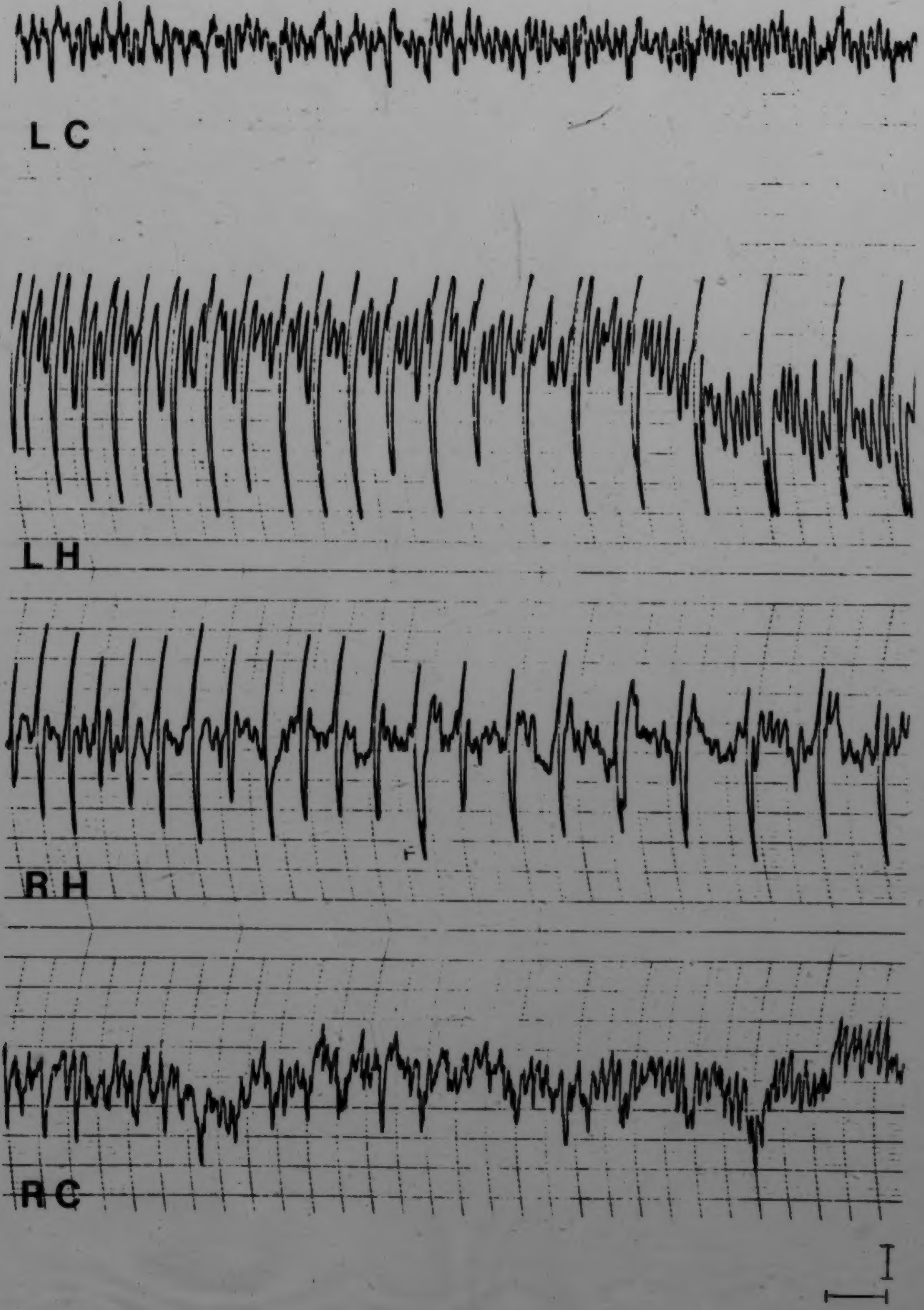

LC
LH
RH
RC

Figure 19. 4-Channel KCl-Injected EEG Record for Subject PSD-3: Example of hippocampal spiking without cortical following.
Record obtained after bilateral injection of 1.3 microlitres of KCl, 450 seconds after the beginning of trial 3. Note there is no cortical following, and that the frequency of spikes is quite low when compared with those in Figures 18 and 15.
LC - Left Cortex, LH - Left Hippocampus
RC - Right Cortex, RH - Right Hippocampus
Calibration: 1 sec and 200 microvolts.


L C
L H
R H
R C

was a fair amount of variation in the records, no baseline record showed the typical high-amplitude spiking, either singly or in bursts, which was seen after the KCl injection. (It appears that the hippocampal records in Figure 14 contradict this statement, but comparison with the KCl induced spikes shown in Figures 18 and 19 shows that the baseline spikes are not nearly as violent.) It can be seen from the baseline records that frequent theta-like activity occurred, indicating further that the electrodes were located in the hippocampus. Cortical baseline records can also be seen to exhibit periods of low frequency synchronous waves as well as cortical desynchrony.

KCl Injection Records

KCl-induced changes of the hippocampal activity usually affected up to three features of the EEG record. Examples of KCl-injected records are given in Figures 9, 11, 13, 15, 17, 18, and 19. Most commonly the records showed high-amplitude spikes (see Figures 18 and 19), either singly or in trains which were quite prolonged. Also visible decreases of amplitude and also frequency were often exhibited. Figure 9 provides a good example of markedly decreased frequency in all four channels following injection of a total of one microlitre of KCl solution. Figure 11 shows a similar change after only 0.3 microlitres. Dramatic decreases in amplitude after only 0.3 microlitres are illustrated in Figures 13 and 16.

On the basis of these changes each record was arbitrarily scored for the presence of visible disruption of normal hippocampal activity. Each record was assigned a value ranging from one, meaning excellent evidence of disruption, to five, meaning very poor evidence of disruption. All the figures presented above which were obtained under the influence of KCl (Figures 9, 11, 13, 15, 17, 18, 19) are examples of records which were assigned a score of one. Comparison of all these figures with their respective baselines, where possible, shows a dramatic change under KCl. Table 2 presents the summarized evaluations of all records. It can be seen from this table that subjects exhibited reliable evidence of hippocampal disruption on all trials. One other important result is presented in Table 3. This Table shows the summarized data concerning amount of KCl injected per trial. A fairly narrow range of total amount injected was obtained. It is important to note also that the maximum amount on any trial was only 1.8 microlitres delivered over a ten minute trial.

The cortical KCl-induced records were also examined for the presence of cortical spikes occurring simultaneously with hippocampal spikes. In general, cortical following was found, not only with spikes but also with changes of hippocampal frequency and amplitude. Figures 9 and 11 show cortical following of hippocampal low frequency waves, while Figure 13 shows amplitude following. Figure 17, in contrast, shows cortical following of spikes. It should be pointed out, though, that this was not always the case. In fact,

	DAYS									
	PRECOND						COND	TESTS		MEAN
	1	2	3	4	5	6	9	11	13	
LI								1.3		1.3
LIC								1.4	1.3	1.3
PSD	1.8	1.3	1.4	1.8	1.6	2.2		1.2		1.6
LSD							1.6	2.0		1.8
PLSD	2.1	1.9	1.6	2.1	1.5	2.1	1.6	1.3		1.9

TABLE 2. Summary Of Arbitrary Scoring Of Hippocampal Disruption Over Days
Each value is the mean arbitrary score for all subjects per group on each day they received HSD. Note that the range of values is from 1.2 to 2.2. Since a value of 1 was signified excellent evidence of hippocampal disruption, it can be seen that the KCl injections produced reliable hippocampal disruptions on all trials.

	DAYS									
	PRECOND						COND	TESTS		MEAN
	1	2	3	4	5	6	9	11	13	
LI								.6		.6
LIC								.4	.6	.5
PSD	.5	.9	.6	.7	.6	.8		.5		.7
LSD							.7	.6		.7
PLSD	.6	.9	.7	.9	.7	.7	.8	.5		.7

TABLE 3. Summary of Amount of KCl Injected Per Trial For All Groups And Subgroups.
Values represent the mean amount injected per group, based on amounts for left and right cannulae for each subject. The range of the amounts upon which these scores are based was from 0.2 to 1.8, so it can be seen that a fairly small amount of KCl was all that was required to produce reliable hippocampal disruption.

often the two hippocampi would show contrasting EEG records, as Figures 11 and 15 show. In this case spikes in one side are not present contralaterally. Figure 17 provides another example of this. Finally Figure 19 shows hippocampal agreement for the most part, with no cortical spiking to match. Thus it can be seen that although it is clear that disruption has occurred, the pattern and form of the disrupted activity varies a great deal, even within a single record. Finally, as mentioned previously, HSD was present throughout each trial, but no records were taken of its absolute duration following a trial.

C. Retention Tests

Licking Rates On Day Eight And Weight Loss Data

Since all subjects received two trials to become familiarized with the drinking tube prior to the conditioning trial, a measure of baseline drinking rate for each subject was obtained from the eighth experimental day. Table 4 presents the range, mean, standard deviation, and standard error of the mean for each of the five groups for the time taken to take ten additional licks after the first 100 licks on this day. The table shows that the groups initial drinking rates were not significantly different, and that the rate is quite fast.

Also the total weight loss data for all groups is similarly summarized and presented in Table 5. Also an independent t-test between the highest and lowest means for

GROUPS	TOTAL	MEAN	S.D.	S.E.M.
LI	14.8	1.9	.7	.3
LIC	14.6	1.8	.8	.3
PSD	13.9	1.7	.5	.2
LSD	16.3	2.0	1.5	.5
PLSD	25.6	3.2	2.3	.8

Table 4. Summary of Baseline Drinking Rate in Seconds for All Groups.

GROUPS	TOTAL	MEAN	S.D.	S.E.M.
LI	746	93.0	19.3	6.8
LIC	747	93.0	13.3	4.7
PSD	649	81.1	27.0	9.6
LSD	610	76.3	24.5	8.7
PLSD	533	69.1	20.3	7.2

Table 5. Summary of Weight Loss Data in Grams Over All Experimental Days For All Groups.

any group revealed no significant differences.

Overall Retention Tests

Table 6 presents the summarized mean licking times over all tests for groups and subgroups. (In Figures 20 through 25 and in the Appendix the ordinate represents the mean time taken to complete ten additional licks after the first 100 licks. Thus the ordinate may also be viewed as representing a measure of suppression of licking, with the level of suppression increasing as average time increases.) Figures 20 and 21 present the suppression functions for the subgroups without HSD and with HSD respectively. Figure 20 presents the initial suppression level and rate of decay over the three tests for all no HSD subgroups. A highly significant Groups x Tests interaction was obtained ($P<.001$), but individual analyses on the functions of subgroups LI-N and LIC-N indicated that the decay rates for these two subgroups did not differ. The significant interaction is therefore most likely due to the floor effect imposed by the poor suppression of the subgroups PSD-N, LSD-N, and PLSD-N.

A highly significant Subgroups x Tests interaction was also obtained ($P<.001$). It can be easily seen from Figure 21 that this result is due to the marked decline in suppression which occurred for most subgroups with HSD on Test Two. Certainly the functions for subgroups LIC-SD and LSD-SD show a striking decline on Test Two followed by an equally striking reestablishment of high suppression levels on Test

GROUPS	DAY 8	TEST1	TEST2	TEST3	TEST4	TEST5
LI-N	2	148	55	11		
LI-SD	3	196	16	52		
LIC-N	2	299	270	205		
LIC-SD	2	300	22	296	16	285
PSD-N	2	33	25	12		
PSD-SD	2	47	4	8		
LSD-N	1	2	2	3		
LSD-SD	3	151	3	151		
PLSD-N	2	4	3	3		
PLSD-SD	5	15	91	11		

Table 6. Mean Licking Times for Subgroups Over Familiarization Day 8 and Tests One to Five.

Figure 20. Mean Licking Time For All Subgroups Which Did Not Receive HSD On Test Two Over Tests One To Three.
This figure presents the initial differences on Test One and also the rate of decay of suppression over the three tests for all subgroups with no HSD (-N).

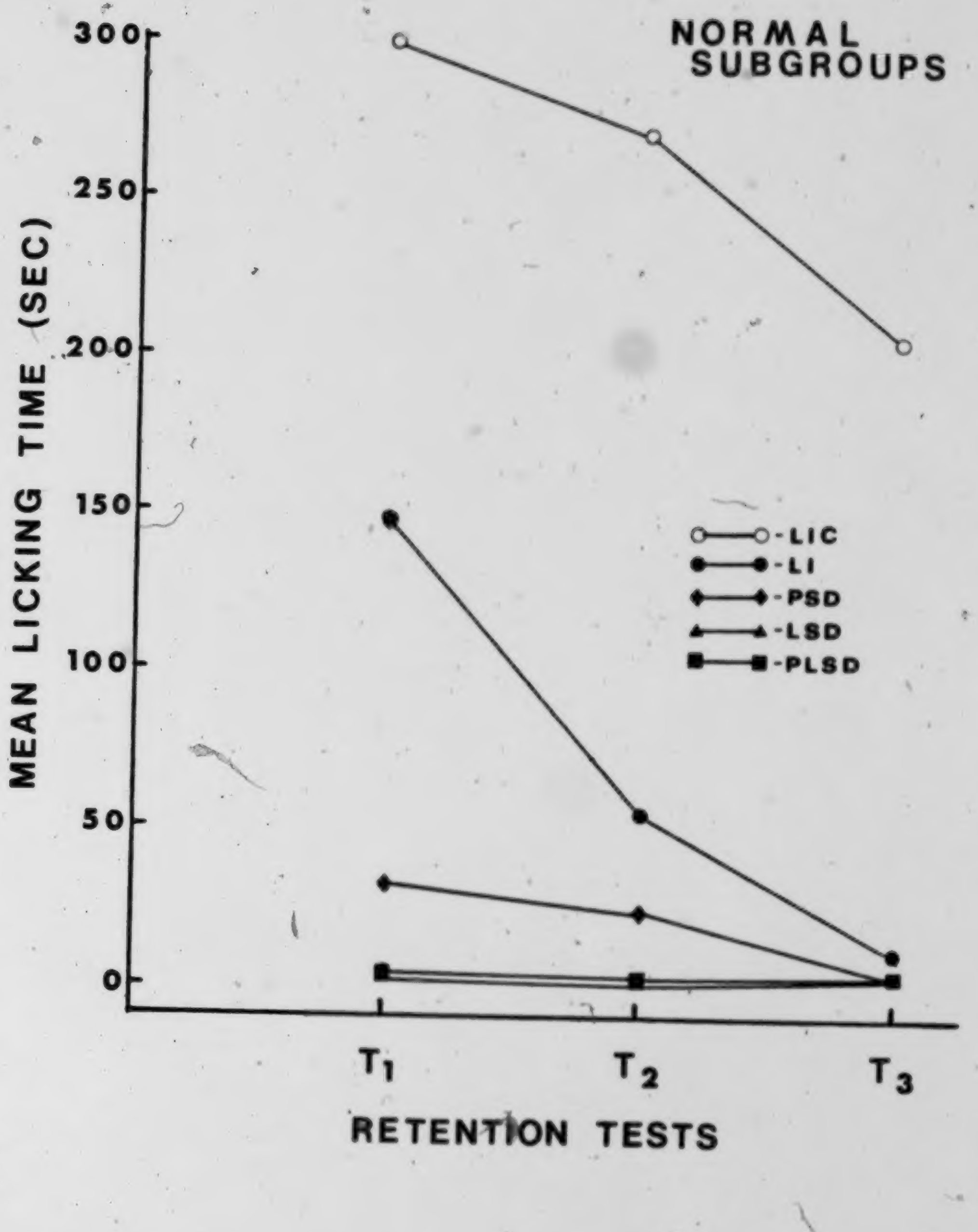
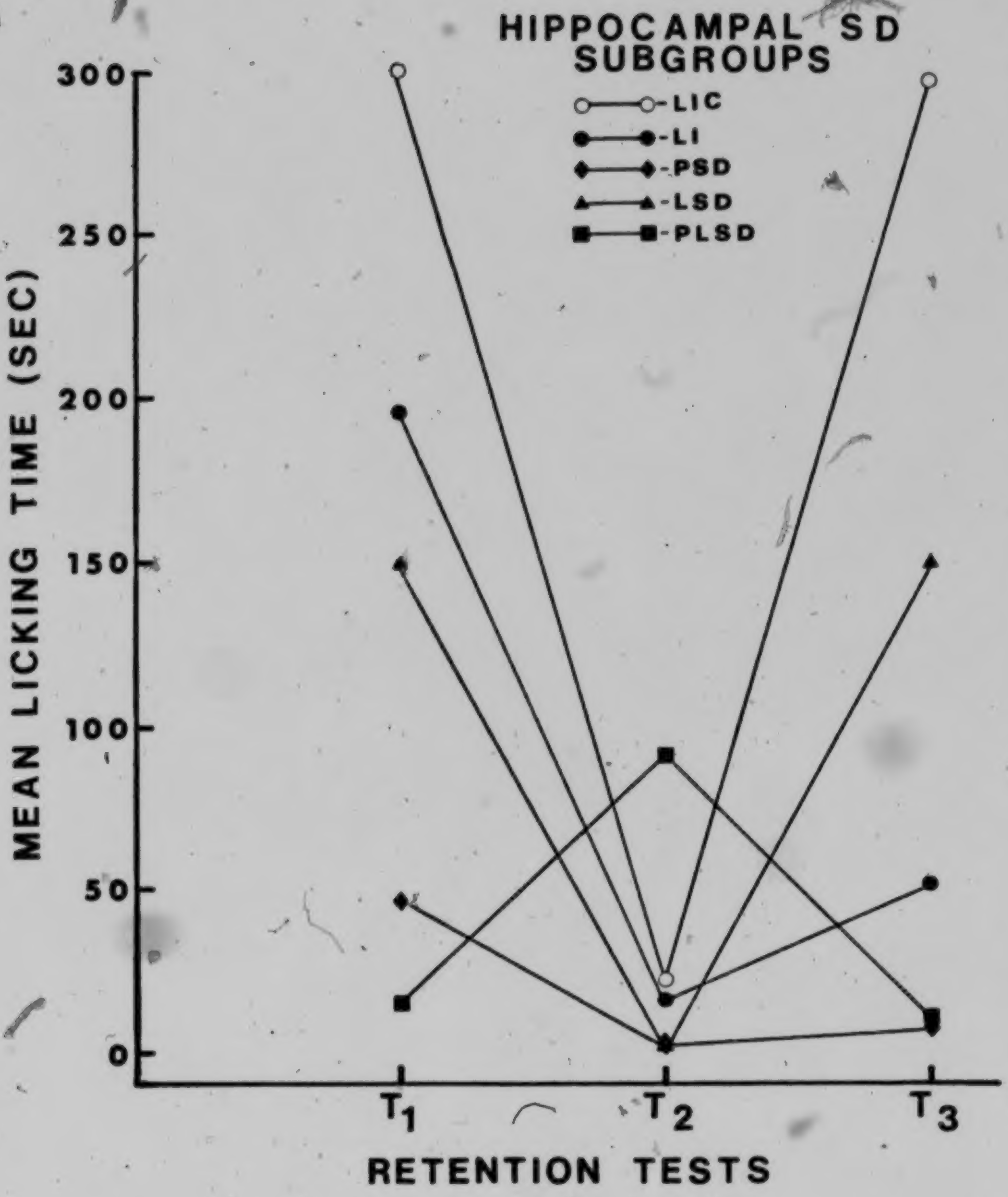

NORMAL SUBGROUPS
MEAN LICKING TIME (SEC)
300
250
200
150
100
50
0
T1
T2
T3
RETENTION TESTS
○—○-LIC
●—●-LI
◆—◆-PSD
▲—▲-LSD
■—■-PLSD

Figure 21. Mean Licking Time For All Subgroups Receiving HSD On Test Two Over Tests One To Three.
Note the dramatic decrease in licking times for groups LIC-SD, LI-SD, and LSD-SD, on Test Two. Also note the striking recovery exhibited by these subgroups, and the paradoxical result for subgroup PLSD-SD.


HIPPOCAMPAL SD SUBGROUPS
○—○-LIC
●—●-LI
◆—◆-PSD
▲—▲-LSD
■—■-PLSD
MEAN LICKING TIME (SEC)
300
250
200
150
100
50
0
T_1
T_2
T_3
RETENTION TESTS

Three.

Finally consider the function shown in Figure 21 for subgroup PLSD-SD, which showed low suppression on Test One, increased suppression on Test Two while under the influence of HSD, and low suppression once again on Test Three. These findings are somewhat paradoxical in light of the pattern seen with the other subgroups given HSD on Test Two.

Test One

Figure 22 provides mean suppression levels for all groups on Test One. This figure (as well as Figures 23 and 24) is provided to allow a convenient comparison between the HSD and no HSD subgroups for each test.

Duncan's multiple range test revealed that group LIC showed a significantly higher level of suppression than did group LI (P<.05), which in turn showed a significantly greater suppression level than the remaining three groups, PSD, LSD, and PLSD (P<.05). There were no significant differences within these three latter groups, which showed an overall low level of suppression.

The histograms which present the raw data (see Appendix) are instructive at this point, since it can be seen that the elevated mean for group LSD is due to two subjects (1 and 2) which, for some reason, obviously demonstrated a CER. The rest of the subjects in the group equally obviously showed no evidence of a CER. In addition, it is important to note that subjects in group LIC showed little variation, achieving a consistently high level of

Figure 22. Mean Licking Time For All Subgroups On Test One.
Note that the subgroups are identical in terms of treatment, since the HSD occurs on the next test. Also note the consistently high suppression of subjects in Group LIC.

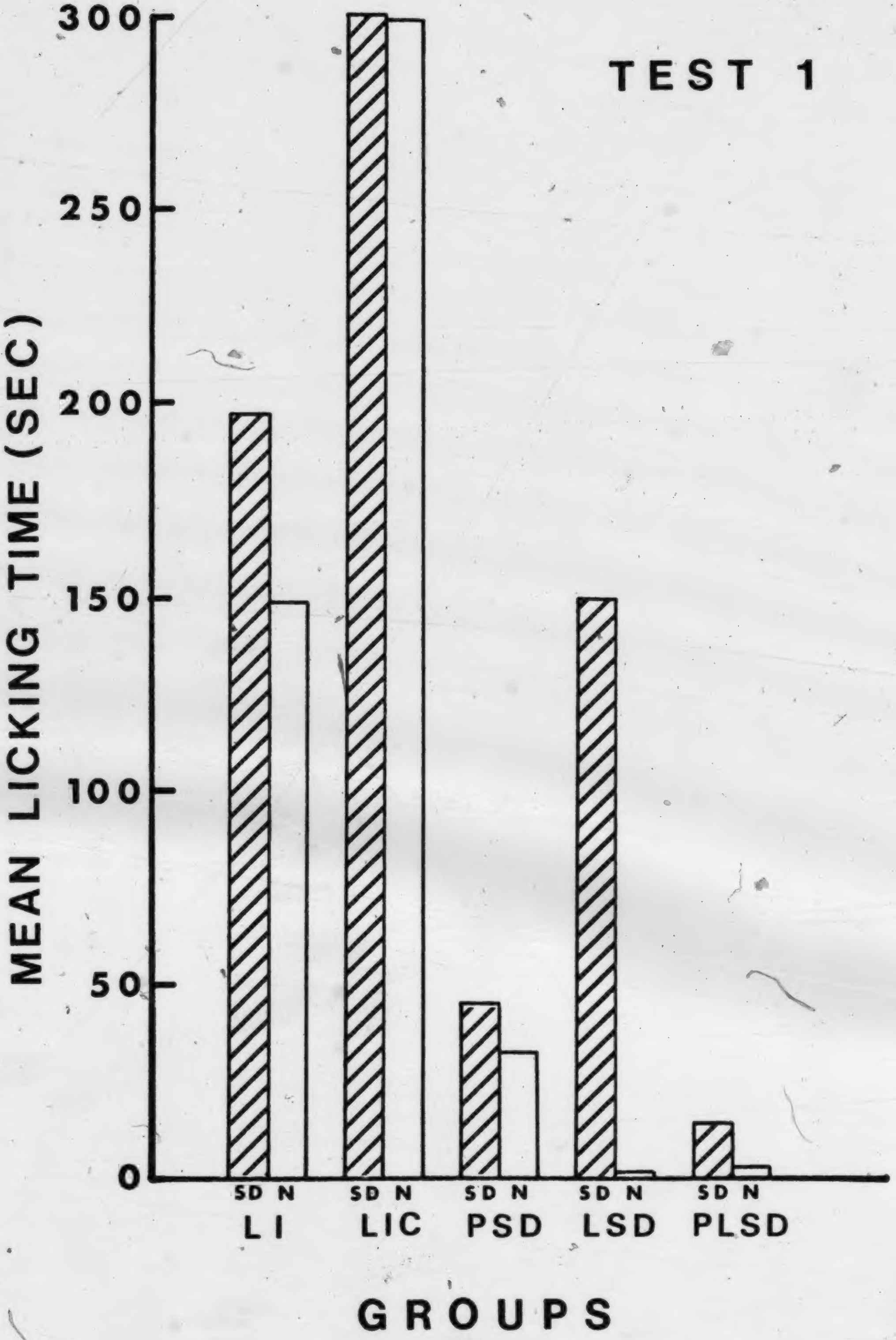

TEST 1
MEAN LICKING TIME (SEC)
300
250
200
150
100
50
0
SD N
LI
SD N
LIC
SD N
PSD
SD N
LSD
SD N
PLSD
GROUPS

Figure 23. Mean Licking Time For All Subgroups On Test Two.
Note that all -SD subgroups show little suppression, except PLSD-SD. Also note that subgroup LIC-N maintains a high level of suppression.

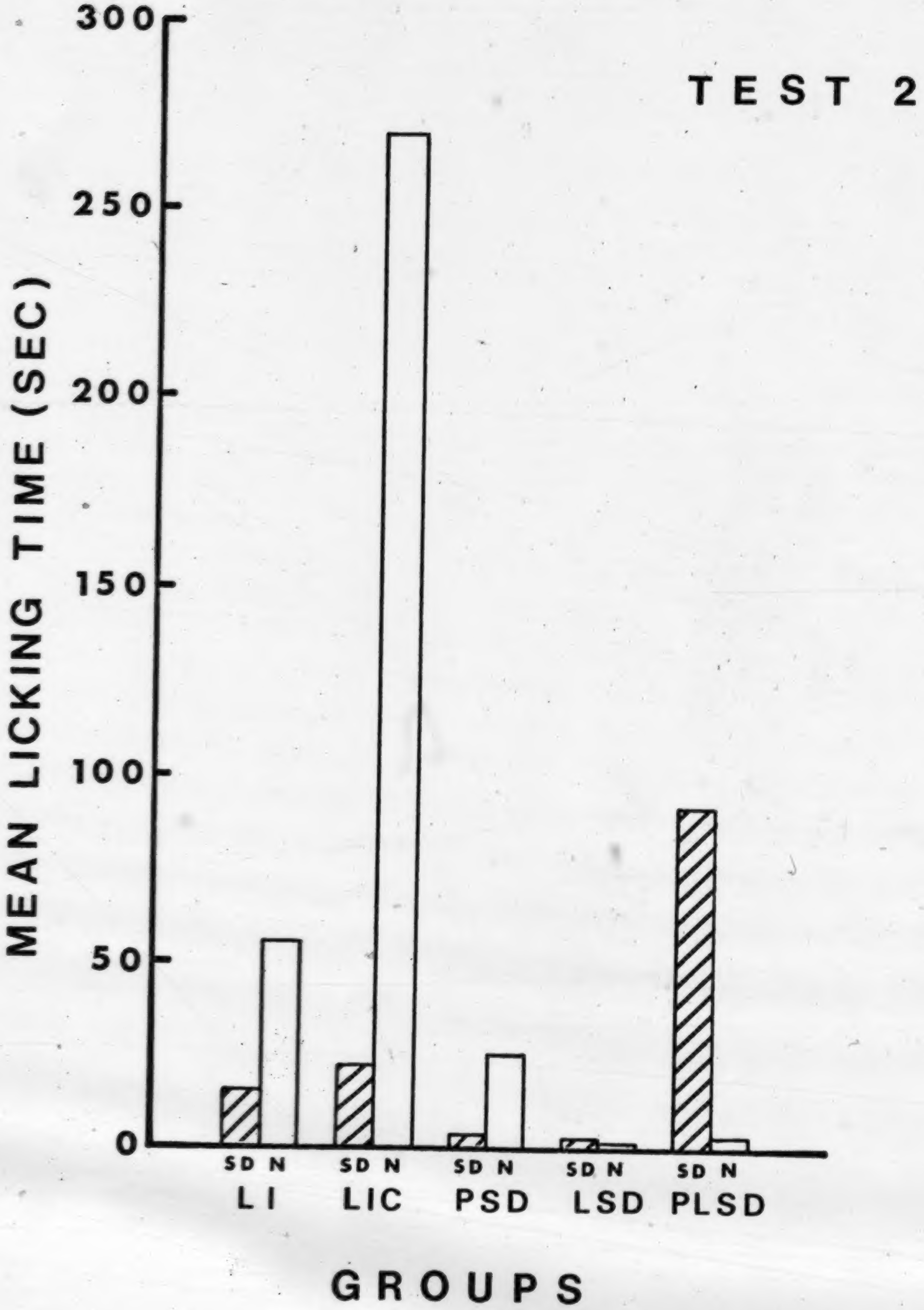
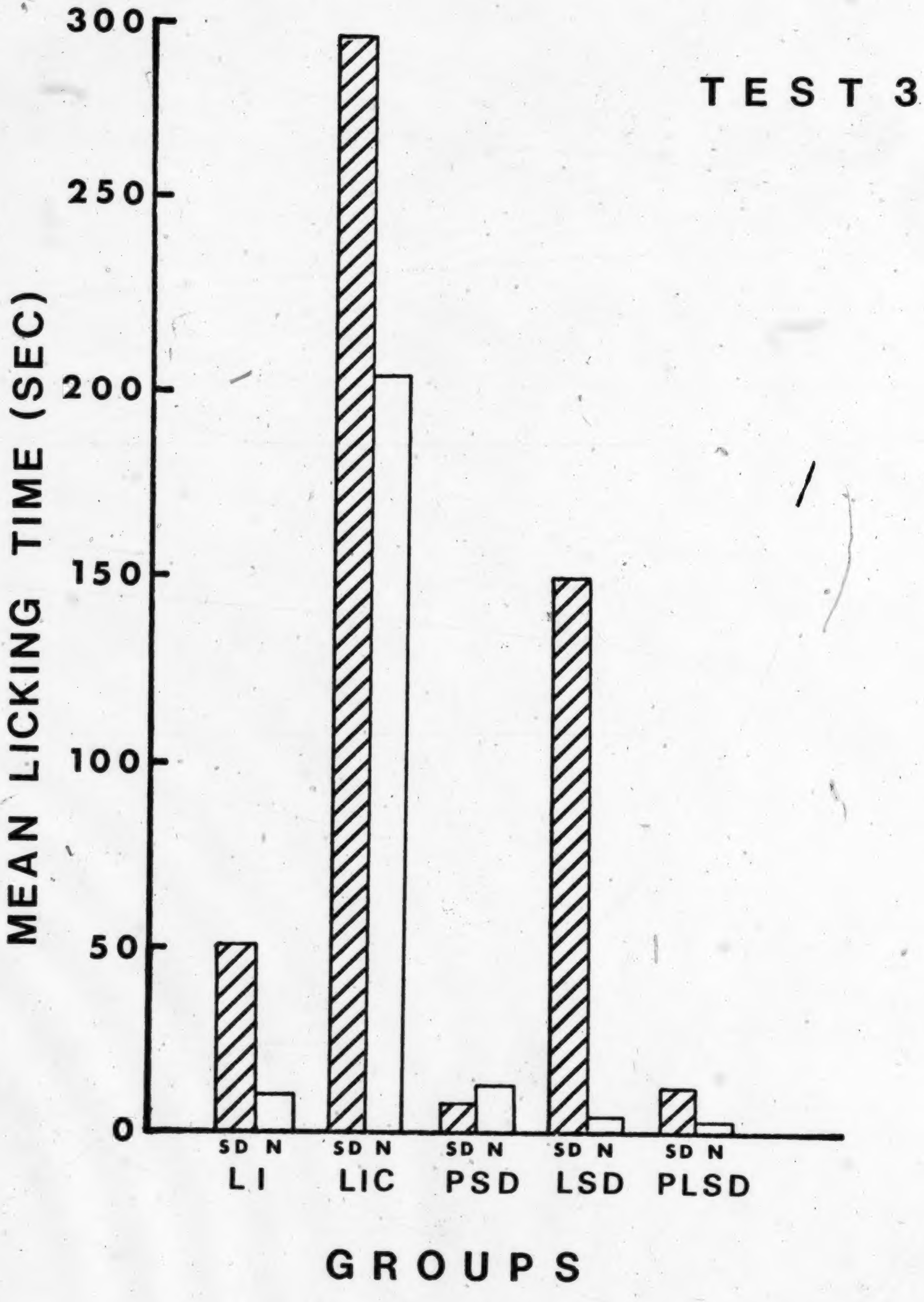

TEST 2
MEAN LICKING TIME (SEC)
300
250
200
150
100
50
0
SD N
SD N
SD N
SD N
SD N
LI
LIC
PSD
LSD
PLSD
GROUPS

Figure 24. Mean Licking Time For All Subgroups On Test Three.
Note the striking recovery of subgroups LIC-SD and LSD-SD. Also note that the suppression level of subgroup LI-N is very low, indicating that near complete decay has occurred.


TEST 3
MEAN LICKING TIME (SEC)
300
250
200
150
100
50
0
SD N
LI
SD N
LIC
SD N
PSD
SD N
LSD
SD N
PLSD
GROUPS

suppression.

To summarize then, group LIC had the highest level of suppression, followed by group LI, followed by the subset of groups PSD, LSD, and PLSD, which showed no evidence of a CER.

Test Two

The results for the Duncan's multiple range test for Test Two revealed that subgroup LIC-N showed a significantly higher level of suppression than any of the remaining subgroups (P<.05). There were no differences on Test Two between any of the remaining subgroups. Thus it was found that on Test Two only subgroup LIC-N, which was not exposed to HSD, maintained a high level of suppression, as Figure 23 illustrates.

Examination of the individual data (see Appendix) for Test Two indicates that regardless of subgroup, any subject in an HSD subgroup which showed a high level of suppression on Test One, was markedly impaired on Test Two, while under the influence of HSD.

Finally it can be seen from the individual data for subgroup PLSD-SD that the suppression level of some individuals rises on Test Two, accounting for the rise seen in the function for this subgroup in Figure 21.

Test Three

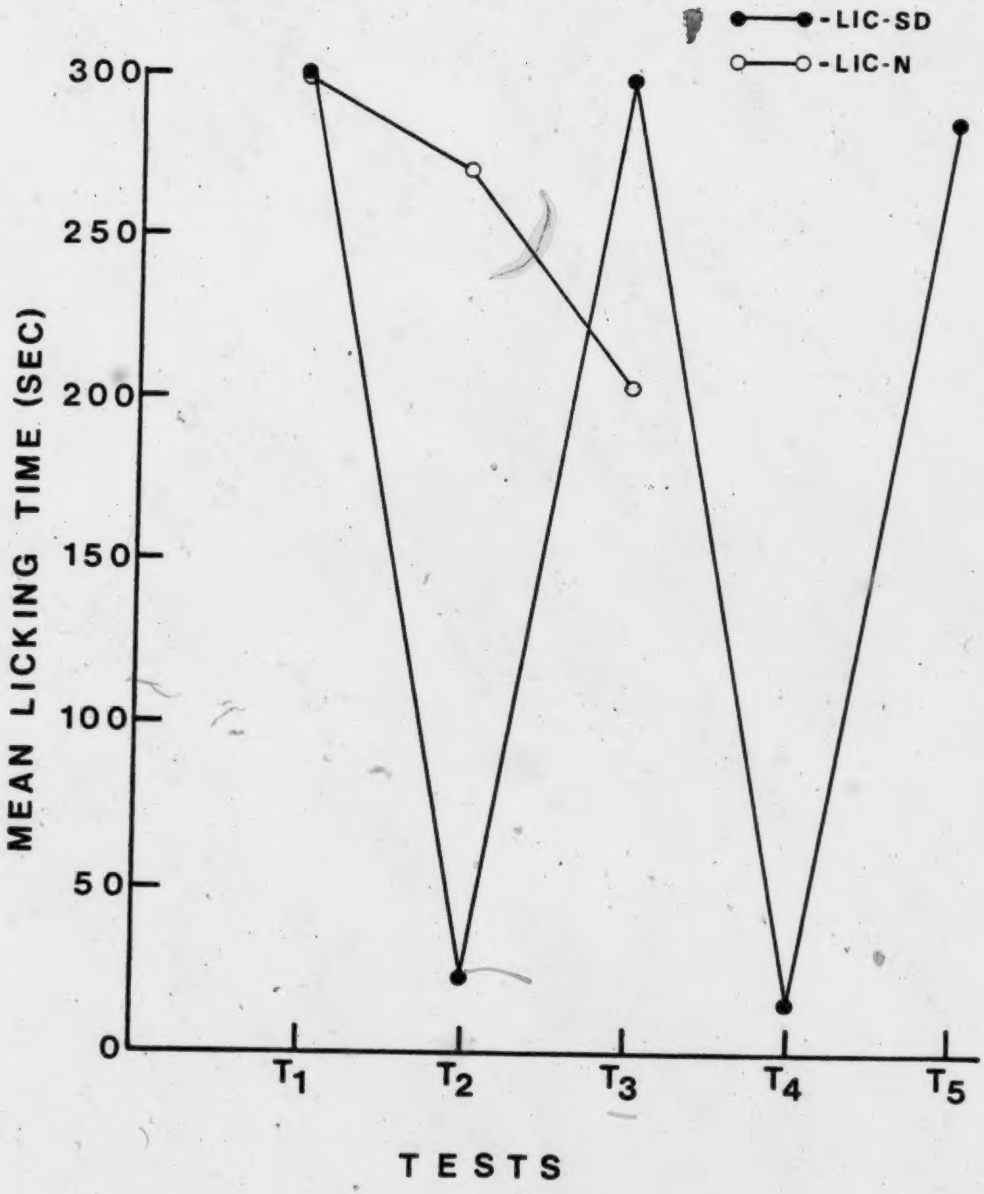
The results of Duncan's multiple range test for Test Three revealed that a subset of three subgroups, LIC-N, LIC-SD, and LSD-SD, showed significantly higher suppression levels than the remaining subgroups (P<.05). There were no differences within either of the two subsets of subgroups produced by this initial division. Figure 24 presents the subgroup means for Test Three. It can be seen from this figure that subgroup LIC-SD reestablished its former high suppression level when no longer under the influence of HSD. This also is the case for subgroup LSD-SD which contained two subjects which showed maximum suppression on Test One (see Appendix). Finally it is important to note that both LI subgroups no longer showed high levels of suppression on Test Three.

Tests Four And Five For Subgroup LIC-SD

Since such a dramatic impairment of suppression resulted from the effects of HSD on Test Two for subgroup LIC-SD, and such a dramatic recovery occurred on Test Three, this subgroup was run for two additional tests, under HSD on Test Four and normal on Test Five, to see if a similar pattern of impairment followed by recovery was obtained.

The results of these additional tests are provided in Figure 25, from which it can be seen that such a pattern did reoccur. In fact, it should also be noted that the recovery level obtained on Test Five was surprisingly high.

Figure 25. Mean Licking Time For Subgroup LIC-SD Over Tests One To Five.
Note the repeated pattern of impairment followed the next test by recovery to very high suppression levels. Also note that appreciable decay has occurred in subgroup LIC-N by Test Three.


●—● - LIC-SD
○—○ - LIC-N
MEAN LICKING TIME (SEC)
300
250
200
150
100
50
0
T1
T2
T3
T4
T5
TESTS

IV. Discussion

A. Electrophysiology And Histology

It is clear from the sample records provided that the injection of KCl solution into the hippocampus produced dramatic impairment of ongoing normal hippocampal activity during the trial. It can also be seen from the records presented that the hippocampal activity prior to each trial was normal and had recovered from any previous KCl injections. Thus it can be concluded that the technique of inducing HSD with KCl was effective in producing a temporary disruption of hippocampal activity, since the effects probably spread throughout the hippocampus. Another important finding was that of cortical following of hippocampal activity of all kinds. This may perhaps be explained by the fact that visible cortical electrode marks could be seen in the brain sections, hence the cortical electrodes were perhaps too near the hippocampus and were actually recording the same hippocampal activity as the cannulae. Cortical electrode impressions of this type, extending into the middle layers of the cortex, were found on a number of subjects and were also clearly visible when the brain was initially removed after perfusion. There are alternatives, however. A study by Macadar, Chalupa, and Lindsley (1974) reported that inducing hippocampal theta rhythms through stimulation of brain stem loci sometimes produced cortical following of the dominant hippocampal rhythm, although usually hippocampal theta was accompanied by cortical desynchronization. This discovery of cortical following of hippocampal activity suggests that the similar findings in the present study may be due to the same phenomenon. In other words, perhaps the cortical following is not an artifact due to experimental error in electrode placement, but is instead produced by ascending influences from the septal pacemaker area and other brainstem loci. The fact that this cortical following was not always present, even in the same subject, suggests that this finding cannot be accounted for solely by placement error, although this factor probably does play a minor role.

There is also the problem of attributing the obtained results in this study to the disruption of hippocampal activity only. Unfortunately an isolated area in the brain does not exist. Obviously each area within the brain exerts a strong influence on the other areas with which it is connected, both directly and indirectly. Consequently it is extremely difficult to precisely localize the effect of a given intervention in normal functioning.

Certainly the hippocampus is no exception to this problem. In fact, the problem is probably more severe in the case of limbic system structures, since they are all major structures, inter-connected with each other. Hence disruption of hippocampal activity must produce marked changes in the activity of neighbouring limbic system structures and in the cortex. Each of these changes then becomes a possible candidate for the agent producing the obtained behavioural impairment, and the question of how to eliminate the alternatives must be discussed.

Some earlier findings are relevant at this point. Kapp (1971) compared the effects of HSD and CSD in CER conditioning in a design similar to the present one, and found that neocortical SD alone was not sufficient to produce retention impairments in rats. Kapp (1971) also reported similar cortical following of hippocampal activity. He concluded that the neocortical effects of HSD were not responsible for the retention deficits he found.

More direct evidence comes from Kesner and Doty (1968), who reported the results of an experiment designed to determine whether post-trial neuro-electrical disruption of other limbic areas would produce retention deficits. They found that retention deficits were produced by post-trial stimulation of the dorsal hippocampus and the amygdala, but not of the ventral hippocampus, mesencephalic reticular formation, and septum.

A variation on the problem of the effects of activity changes in neighbouring structures is also relevant. In addition to these changes being due to the changed hippocampal activity itself, the possibility that diffusing KCl might have directly altered the activity of surrounding areas must also be considered. However, several factors make this unlikely. First it has already been reported that HSD does not spread beyond the boundaries of the hippocampus

(Bures, Buresova, & Weiss, 1960). Second the quantity of KCl injected was very small, and was injected quite slowly. Previous studies have shown that the spread of agents into surrounding tissue in the brain bears a direct relationship to the volume injected (Myers, 1966). Injected volumes of 1.0, 3.0, and 4.0 microlitres of Evans' blue dye produced average spreads of 0.9, 2.9, and 3.7 mm respectively. Since in the present study the maximum volume injected in any trial was only 1.8 microlitres over ten minutes, it is relatively safe to assume that the injected KCl remained in the hippocampus. Furthermore the method employed to inject the KCl makes it possible that the actual figures given may be slightly inflated. Undetected air bubbles in the polythene tubing may have been compressed when the plunger on the syringe was depressed, resulting in less KCl actually being injected. Also some of the KCl which was injected may have entered the space between the inner and outer cannulae, instead of entering hippocampal tissue. This combination of factors strongly suggests that the KCl involved in this study was, in fact, localized within the hippocampus.

Although this evidence is highly suggestive that the major area responsible for the present results is the hippocampus, it is impossible to justify a firm conclusion to this effect. More studies concerning localization of the effects of neural intervention must be added to the relatively meagre current number, and definite conclusions regarding this problem must await these additions.

Unfortunately, there are some quite serious problems relevant to the interpretation of the histological results. Due to time constraints, and occasional lack of facilities, the sacrificing of the subjects did not commence until approximately three weeks after the end of the experiment, and the subsequent perfusions were not completed for another three weeks. This allowed ample time for the development of lesions and infection-induced damage, which has been shown to have occurred (see Figure 7). The problem which this introduces is that it is impossible to tell directly whether these lesions occurred before, during, or after the experiment. However when the data for those subjects which obviously had suffered this kind of damage was removed, the corrected overall analysis and the multiple range tests were no different from the initial analyses based on all the subjects. This raises two encouraging alternatives. First the lesions were not present during the experiment and could not have affected the data, or second, the lesions were present and did not affect the data. Given the size and extent of the damage (notice that the sections shown in Figure 7 for subjects PSD 5 and LSD 1 show extensive damage of the diencephalon), it is difficult to conclude that such a lesion, if present during the experiment, would have no effect. For this reason the results presented have been based on the analysis of data for all subjects.

B. Test Results

The first finding to be discussed is the data for Test One for all subjects. As expected a latent inhibition effect was obtained for the LI group since it showed significantly poorer suppression than the control group LIC. Also, although the rate of the decay for the functions of these two groups do not differ, by Test Three group LI showed very poor suppression, while group LIC remained at a fairly high suppression level. Thus it can be concluded that fairly strong evidence of a latent inhibition effect was obtained. However it is worth mentioning at this point that the latent inhibition effect was subtantially weaker than that obtained by Carlton and Vogel (1967) who found virtually no suppression in rats exposed to a similar procedure. A possible, but unlikely, explanation for the difference is that in this study subjects had undergone sham operations, which may have caused sufficient hippocampal damage to interfere with the establishment of the latent inhibition effect. Perhaps more likely is the fact that the training procedures were different, particularly with respect to the drinking regimen employed by the two studies. To be specific, Carlton and Vogel (1967) gave only a single water tube familiarization trial, and no drinking cage training.

It can also be concluded that good CER conditioning occurred in group LIC, in agreement with initial predictions. However it is equally clear that group PLSD did not produce the expected result of high levels of suppression. It will be remembered that this group was intended to emulate irreversibly lesioned groups by inducing HSD during preconditioning and conditioning. Contrary to predictions, this group showed severe impairment of acquisition of a CER, as did groups PSD and LSD overall, even though two subjects of the latter group did show maximum performance.

The most parsimonious explanation of the results for these three groups is that HSD induced during preconditioning and/or conditioning produces impaired acquisition of the CER. Unfortunately the fact that no significant differences exist among these three groups means that no conclusions may be drawn concerning the relative importance of an intact hippocampus during the preconditioning or conditioning phases in producing the latent inhibition effect which characterizes normal animals.

Several alternative explanations for these results present themselves, but the overall pattern of the results introduces difficulties for each of them. For example, one may wish to attribute the lower suppression level to a latent inhibition effect in all three cases. In other words, perhaps the low suppression is due to a normal preconditioning interference effect, and disrupting hippocampal activity had no effect during these phases. If this is to be seriously considered two concerns must be dealt with. First, damage to the hippocampus would be expected to block a latent inhibition effect and raise suppression levels, according to all reports in the literature and according to the attentional hypothesis. This is so because presumably the hippocampal mechanism which underlies the normal occurrence of interference resulting from a previous irrelevant association is non-functional during the pre-conditioning phase. However, the present data suggest that, in fact, the proposed latent inhibition effect is facilitated, ie. interference is increased, in any group receiving HSD, to the point where it is substantially stronger than that shown by the LI group. Unfortunately no control was run to directly test whether a result of failure to suppress licking was due to a latent inhibition effect or to simple impairment of CER conditioning, since there was no *a priori* reason to suspect that CER conditioning might be impaired. In hindsight, it can be seen that a sixth group of subjects given no preconditioning and HSD during CER conditioning would have been most instructive and valuable in determining whether impairment of CER conditioning was produced by HSD during the conditioning phase.

The second concern relates to the effect of HSD. It seems highly unlikely that HSD and lesions should produce such different effects. Lesions have been shown to block latent inhibition (Ackil *et al*, 1969; McFarland *et al*, 1978), hence it is unlikely that HSD should produce the opposite effect of apparently facilitating latent inhibition. For these two reasons, a latent inhibition interpretation of the low suppression exhibited by groups

PSD, LSD, and PLSD is untenable, although tempting at first consideration.

A second alternative explanation involves the phenomenon of state-dependent learning. According to this approach performance would be impaired in those animals which formed the initial association under one internal state and were subsequently required to perform under a different internal state. In the present case this would imply that subjects which learned under HSD would be expected to show the highest level of suppression when once again under the influence of HSD. This alternative is tempting in that it provides a feasible explanation for the paradoxical result obtained for those few subjects in subgroup PLSD-SD which showed low suppression on Test One and Test Three, but showed increased suppression on Test Two when once again under the influence of HSD. A difficulty with this interpretation arises, though, when one examines the results for subgroup LSD-SD, which also formed the original association while under the influence of HSD. Not only were the results for this subgroup opposite those for subgroup PLSD-SD, but they were also in good agreement with the remaining subjects which showed high suppression on Test One, and impairment on Test Two, when affected by HSD. Also since subgroup PSD-SD did not learn under HSD the state-dependent learning prediction would be that this subgroup would show good retention when tested under normal conditions, a finding which clearly did not result. Hence a state-dependent learning approach runs into a substantial amount of difficulty, although it does fit some of the results.

It seems then, that the only remaining alternative which will satisfy all the results is the one first mentioned, namely that HSD during any of the initial learning phases impairs simple acquisition of the CER in the rat. Unfortunately it is no easy task to postulate why this might be, or even to state whether such a finding agrees with the literature, since it is extremely sparse on this subject. Those reports which have appeared complicate matters more, since the conclusions they contain are contradictory.

In a distantly related paradigm, for example, Isaacson, Douglas, and Moore (1961) reported facilitated acquisition of a conditioned avoidance response in lesioned rats. In their report they cited, in support of their own conclusions, a study by Brady and Hunt (1955) which reported no impairment of CER acquisition following hippocampal ablation in rats. However the actual review article by Brady and Hunt (1955) reported the finding that bilateral injury of the hippocampus attenuated the "anxiety" response in several animals and apparently made it impossible or unusually difficult to recondition (Brady & Hunt, 1955, p. 318). Clearly this implies a finding of impairment, both in initial recall and in facility of reconditioning. It is also interesting to note that the data referred to by Brady and

Hunt (1955) were never published.

The picture is further complicated by a report by Nadel (1968) who found that dorsal and ventral hippocampal lesions in rats had a differential effect on CER acquisition. His study is perhaps more relevant to the present one in that it involved a similar task of lick-suppression following footshock. In any case he found that dorsal lesions facilitated CER acquisition, while ventral lesions were found to be no different from control subjects as far as CER acquisition was concerned. However these results are in sharp contrast to those of Molino (1975) who found that lesions of the postero-ventral hippocampus in rats significantly retarded CER acquisition in adult rats but not in infants. On the basis of such conflicting evidence it is extremely difficult to interpret the present findings. It is worthwhile mentioning that the Nadel (1968) study did not report findings for subjects with the entire hippocampus lesioned. Since HSD probably spreads out to affect the entire hippocampus, it is conceivable that loss of both dorsal and ventral hippocampus might produce results which are more compatible with those presented here.

Two more experiments are relevant to this issue. Schmaltz and Theios (1972) concluded that the typical findings, for lesioned animals, of faster acquisition and slower extinction for a variety of operant tasks, also holds true for classical conditioning paradigms. Similar evidence of no acquisition impairment in taste aversion was reported by Kimble, Bremiller, Schroeder, and Smotherman (1979).

Thus, although the literature is not extensive and is fraught with discrepancies, it apears that the general consensus is that hippocampal damage does not seem to markedly impair CER acquisition. This conclusion is clearly at odds with the present findings, and the need arises to provide some kind of reconciliation of the findings.

Perhaps one fruitful avenue of speculation is to examine results of studies which involve a different kind of interference with hippocampal function. In sharp contrast to lesion study results, studies employing post-trial stimulation of the hippocampus report a common finding of CER acquisition impairment, although once again the literature is fairly sparse.

To begin with, Salafia, Romano, Tynan, and Host (1977) reported that simple acquisition of a nictitating membrane response was markedly delayed by post-trail stimulation of the hippocampus. When conditioned responses eventually began to appear, though, they were unaffected by further stimulation. Although this was not a CER acquisition study, it does serve to indicate an effect on simple conditioning from stimulation. Shinkman and Kaufman (1972) reported more relevant findings in rats exposed to post-trial stimulation which was strong enough to produce seizure-like activity in the hippocampus. An earlier report by Shinkman and Kaufman (1970) had suggested that the effectiveness of such post-trial seizure-inducing stimulation was time dependent, in other words, CER acquisition impairment decreased as the trial-stimulation interval increased. This finding of acquisition impairment has been reported for a number of qualitatively similar tasks, including passive avoidance in rats (Brunner, Rossi, Stutz, & Roth, 1970; Lidsky & Slotnick, 1970; Vardaris & Schwartz, 1970; Kesner & Conner, 1974), and also a finding of impairment due to perseveration in a T-maze (Leaton, 1968), although this latter report was based on a very small number of subjects. McDonough and Kesner (1971) have also reported impaired acquisition following brief electrical stimulation of the hippocampus in cats. Of course, this area of the literature also contains conflicting evidence. Erickson and Patel (1969) found facilitated acquisition of a discriminated lever press avoidance task following hippocampal stimulation, although the stimulation used in their study was of a low intensity. Nevertheless the consensus seems to be that post-trial hippocampal stimulation can produce impaired acquisition of a CER.

It will be remembered that in the previous discussion, findings of seizure-inducing stimulation producing CER acquisition impairment (Shinkman & Kaufman, 1972) were mentioned. Inspection of the records presented in this study of hippocampal activity during HSD also shows that distinct seizure-like activity often occurred during trials. Since electrical and chemical stimulation have both been shown to produce large amplitude synchronous spikes or spike trains, it is proposed that the effects of post-trial stimulation and HSD are qualitatively similar. Hence it is further proposed that the impaired CER acquisition obtained in the present study is due to a similar mechanism to that underlying the impairment produced by electrical stimulation. Certainly the effects of HSD were long-lasting enough to be still present immediately after the single conditioning trial, as Figure 18 illustrates, therefore HSD does qualify as a post-trial stimulating agent. Of course, HSD is clearly a more radical manipulation, since its effects are also present during trials.

One approach to which this explanation seems to be relevant is the memory consolidation literature mentioned in the introductory review. The findings which pertain to this approach all report that learning is highly vulnerable to disruption of normal function which occurs immediately after the learning episode. It seems clear that the disrupting agent HSD can produce consolidation defects (Avis & Carlton, 1968; Hughes, 1969; Kapp, 1971). So too, it seems, can post-trial electrical stimulation. Since this is the case the present use of HSD during learning trials may also have produced a consolidation impairment, as the effects of HSD have been clearly demonstrated to be present after the shock was delivered, and are most likely still present until several minutes after each trial.

It should be noted that a consolidation impairment explanation satisfies the results for groups LSD and PLSD, which were conditioned under HSD, but is inadequate for the Test One results for group PSD which were normal for the conditioning phase. It is unlikely that this result was due to post-learning interference since the baseline records appear normal on each successive trial day for the subjects. The possibilty remains that HSD produced some changes which were not manifested in subsequent records, but the limitations of the present study do not allow further speculation as to what cytoarchitectural or biochemical changes may have resulted from HSD. It should be explicitly pointed out, though, that group PSD received HSD for six successive trials, which may also suggest that some unseen change occurred. It is true that group PLSD received HSD on seven trials, but presumably the consolidation hypothesis is a more powerful explanation for the result for this group.

There still remains a problem, however. The consolidation hypothesis, as originally outlined by Duncan (1949) and McGaugh (1966), is insufficient to account for two types of evidence reported in the literature pertaining to another disrupting agent, electroconvulsive shock (ECS). Findings that ECS given 72 hours *prior* to learning produced 'prograde' amnesia(Poschel, 1957; Adams & Lewis, 1962), and that long learning-ECS intervals of 24 hours (Misanin, Miller, & Lewis, 1968), three days (Geller, Sidman, & Brady, 1955), and even 63 days (Braun, Patton, & Barnes, 1952), also produced amnesia have been reported. The consolidation hypothesis is particularly hard-pressed to account for these findings of prograde amnesia resulting from ECS given prior to the learning trial. It is also stretching the imagination a bit to imagine a consolidation process lasting for three days, let alone 63 days.

In order to account for these discrepancies, Adams & Lewis (1962) suggest that ECS itself is a very strong UCS, the response to which becomes conditioned to various cues associated with the experimental apparatus and training situation in which the experiment is run. They proposed that the neural disruption which is produced by ECS becomes conditioned to the various environmental cues present at the time of ECS administration. Subsequent exposure to the same set of environmental cues in the absence of ECS would then evoke an abnormal pattern of brain activity, similar to that produced by the original ECS, which could then interfere with normal functioning. Such a theory would then account for the amnesic effects resulting from delivery of the ECS prior to learning and also would account for the long learning-ECS interval results of retrograde amnesia, since it is immaterial when the conditioning of this abnormal neural activity occurs.

Adams and Lewis (1962b) performed an elegant direct test of the ECS conditioning hypothesis versus the consolidation hypothesis. Identical amounts of ECS were given to two groups at the same learning-ECS interval. The groups differed only in that one group was given ECS in an different environment from the one it was later tested in, while the other group was given ECS in the same apparatus in which performance was later tested. The rationale behind this experiment was as follows. Since the consolidation hypothesis is concerned primarily with the length of the learning-ECS interval, the two groups would not be expected to differ in the amount of retrograde amnesia they exhibited. On the other hand, if the amnesia was produced by ECS conditioning to the training environment cues, the resulting expectation would be that the group tested in the unfamiliar test apparatus, would exhibit less retrograde amnesia, since there would be fewer cues available to evoke the ECS conditioned response. The results of this experiment supported the ECS conditioning predictions.

The relevance of this hypothesis to the present experiment is easily demonstrated, since it has already been shown that seizure-inducing stimulation and HSD are qualitatively similar disruptive agents. ECS perhaps represents a more intense and certainly more global disrupting agent, but it too produces synchronous spike discharges. In addition, it has already been reported that HSD produced retrograde amnesia at the fairly long learning-HSD interval of 24 hours (Avis & Carlton, 1967; Hughes, 1968; Kapp, 1971), therefore inclusion of HSD in the list of disruptive agents which could act as UCS's is permissible.

It is the evidence concerning ECS prior to learning which is most interesting from the present point of view.

Since it has been mentioned previously that ECS and HSD have similar properties, it is proposed that a similar type of conditioning of abnormal activity to environmental cues could have occurred in the present case, and would be expected to have a similar disruptive effect on normal functioning. If this is so, then perhaps an explanation for the low suppression level of all three experimental groups may be provided. Cue-induced disruption would occur during any trial in any group following the initial administration of HSD. In the case of group PSD, this would mean that, although they did not actually undergo HSD during the conditioning phase, the testing box cues would have elicited a conditioned type of neural activity which would interfere with normal conditioning of the CER. Thus the same mechanism, induced abnormal activity interfering with conditioning, can be proposed to underly the results for all three groups on Test One.

There may also be a further factor underlying the Test One results. Since by Test One all three experimental groups had received HSD, this cue-induced disruption of activity would be expected to be present during any test without HSD. Thus for all intents and purposes, tests without HSD could in reality have been affected by this conditioned disruption, resulting in a similar interference effect to that shown by groups LI-SD and LIC-SD on Test Two. In other words, perhaps the same interference in performance which resulted from HSD during Test Two in those subjects which did show previous suppression on Test One, occurred for the experimental groups on Test One. This would provide two possible reasons for the lack of CER performance shown on Test One for these groups. First initial conditioning could have been interfered with, due to cue-induced disruption of normal functioning during conditioning, and second, since HSD undeniably interferes with suppression, perhaps the cue-induced disruption during testing in the experimental groups had a similar interfering effect. It is interesting to speculate that interference during conditioning could result in the disruption of ongoing consolidation processes. Similarly one process which could be affected by the disrupted neural activity during performance is that of retrieval. This latter subject of performance problems is elaborated upon later in the subsequent discussion of the Test Two results, but for now it should be stressed that a retrieval problem is only one of the alternatives relevant to the effect of HSD on performance. However the present point is that an initial interference with CER conditioning, plus an additional interference with performance, all due to a cue-induced abnormal HSD-like brain state, can account for the low suppression shown by groups PSD, LSD, and PLSD throughout the tests.

However, it remains to be explained why the CER should be interfered with, and not other behaviours which are presumably vulnerable. The question of exactly which associations and responses would be expected to be subject to interference from this cue-induced abnormal brain state is therefore relevant. In terms of associative strength, it is assumed that the response of drinking has a high strength, due to its obvious necessity to the animal, and its prolonged degree of practice. In contrast, the response of ceasing an ongoing behaviour, such as drinking, following a noxious stimulus, while undeniably important to the animal, has had only a single trial, and hence, is presumed to have a substantially lower associative strength. This should make it much more vulnerable to abnormal brain activity occurring when the low association strength response was required. In support of this the results of group LIC-SD on Test Two show that true HSD produces a marked disruption of the suppression response which was strongly exhibited on the previous test. If such is the case for a group which was intact during learning, then it is likely that the associative strength of the suppression response is even less in the three experimental groups which were interfered with during the CER conditioning. Consequently the presumably "milder" disruption effect of the cue-induced HSD-like state would be all that was required to interfere with the even more fragile suppression response.

It is clear then that any conclusions concerning the reasons for the low level of performance on Test One for groups PSD, LSD, and PLSD must be general at best. The hypothesis proposed immediately above is attractive and intriguing alike, but unfortunately it is distinctly *a posteriori*, and hence must await further corroborative empirical support.

Although the Test One results allow only tentative conclusions, the same does not hold true for the rest of the tests, which were designed to investigate the effects of HSD on performance rather than learning. The most important result concerning Tests Two and Three, is that every subject, regardless of group, which showed high performance on Test One, showed a striking decrease while under the influence of HSD on Test Two, followed by an equally striking recovery on Test Three, when no longer under the influence of HSD.

The validity of this pattern is even more forcibly demonstrated by the results for subgroup LIC-SD on additional Tests Four and Five. It is also interesting to note that if the decay function for subgroup LIC-N (see Figure 25) is extrapolated maintaining the same rate of decay, the performance levels which would result on Tests Four and Five, would be well below those for subgroup LIC-SD. In fact this high recovery level suggests that it is as if Tests Two and Four had never occurred for this subgroup. This is further supported if one compares the level reached by subgroup LIC-SD on Test Three with that of subgroup LIC-N on Test Two and similarly for Tests Five and Four. It can be seen that the performance levels are more similar for the two subgroups viewed in this way. However the main point about the LIC-SD subgroup results is that they show that the pattern of impaired performance followed by recovery was replicated. This pattern of impaired performance when the hippocampus is disrupted followed by recovery provides compelling evidence in support of the response inhibition hypothesis of hippocampal function.

However, in general, a behavioural result consisting of impaired performance on a retention test could be due a variety of alternatives. Faulty underlying processes could exist in a) initial learning and consolidation of the association, b) retention of the association in storage, c) retrieving the association, and d) motoric capacity.

In the present case, the fact that unimpaired performance was demonstrated on Test Three, effectively eliminates a fault in learning, consolidation, and retention, as the cause of the impaired performance on Test Two, although it has been suggested that consolidation problems might underly the initial poor performance of subjects on Test One. The alternative of motor dysfunction is also effectively eliminated since subjects were often noticed to drink intermittently while under HSD, thus demonstrating that they were motorically capable of ceasing to drink while under HSD. The elimination of these alternatives appears to point to a simple conclusion, since only one alternative remains, that of retrieval problems. However it is possible to further divide this alternative.

One can to conceive of a situation in which retrieval processes function normally yet performance is still impaired. If one of the functions of the hippocampus is to act as a response sequencing mechanism, or in other words, to evaluate current circumstances and allow only the most appropriate response to be expressed by inhibiting ongoing competing responses, disruption of the hippocampus could then impair the inhibition of responses, which would effectively prevent the expression of the more appropriate response, yielding a behavioural result of impaired performance. In this case unimpaired retrieval processes could be functioning normally, resulting in the appropriate response pattern being summoned, yet not being expressed since the response switching mechanism has been disrupted and ongoing behaviour perseveres, although it is clearly inappropriate.

The results obtained in the present experiment do not allow a further choice between these two alternatives of retrieval processes or response inhibition and behaviour switching processes. However other evidence suggest strong support for the response inhibition hypothesis. For example the findings concerning extinction in lesioned animals are relevant. In this case it clear that subjects are not impaired in retrieval processes, since their behaviour is characterized by an apparent inability to forget (Kimble, 1968). It is likely, then, that these results are due to a problem in response inhibition, a function which is proposed to be mediated by the hippocampus. A similar interpretation may be applied to the findings of perseveration, indistractibility, and lack of habituation in animals with hippocampal damage or disruption. In addition the other tasks which involve response inhibition mentioned in the Introduction are similarly relevant. This body of evidence, seems to decrease the attractiveness of the retrieval deficit hypothesis, since in each case some goal-oriented response is clearly all too well retrieved.

The results of the present experiment lead to two conclusions. First it appears that hippocampal disruption achieved by HSD produces a severe impairment in CER acquisition, possibly due to interference with ongoing consolidation processes following the learning trial. Second hippocampal disruption during performance produces drastic impairment of performance, which recovers when the effects of HSD are no longer present. This second finding seriously undermines the theory that the hippocampus mediates retention of information, while strongly supporting that which attributes a response inhibition role to the hippocampus. In addition it is also possible that an HSD-like pattern of neural activity, which is conditioned to the apparatus cues, can account for the impairment of CER conditioning and subsequent performance alike, during trials in which no HSD is administered, although this hypothesis is clearly *post hoc* and requires independent testing.

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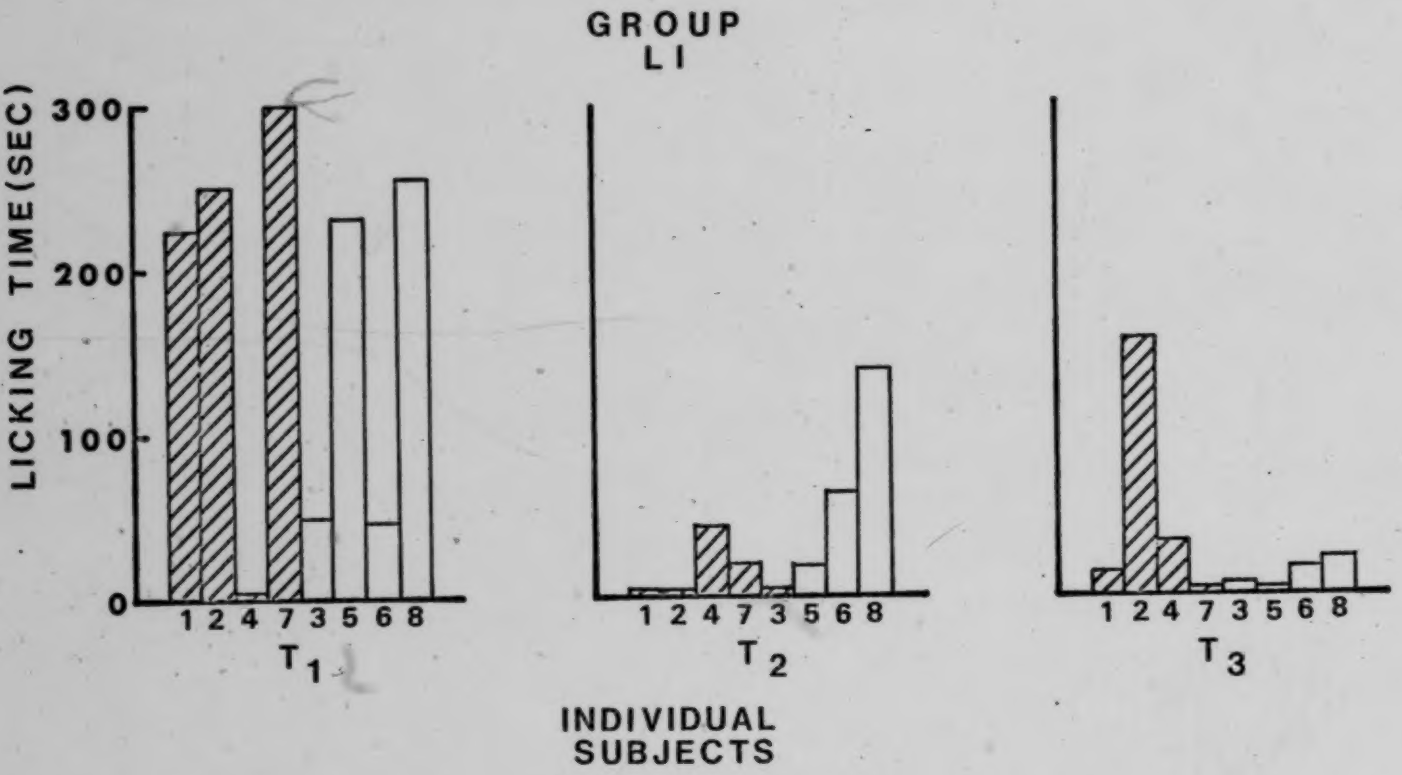
APPENDIX


GROUP
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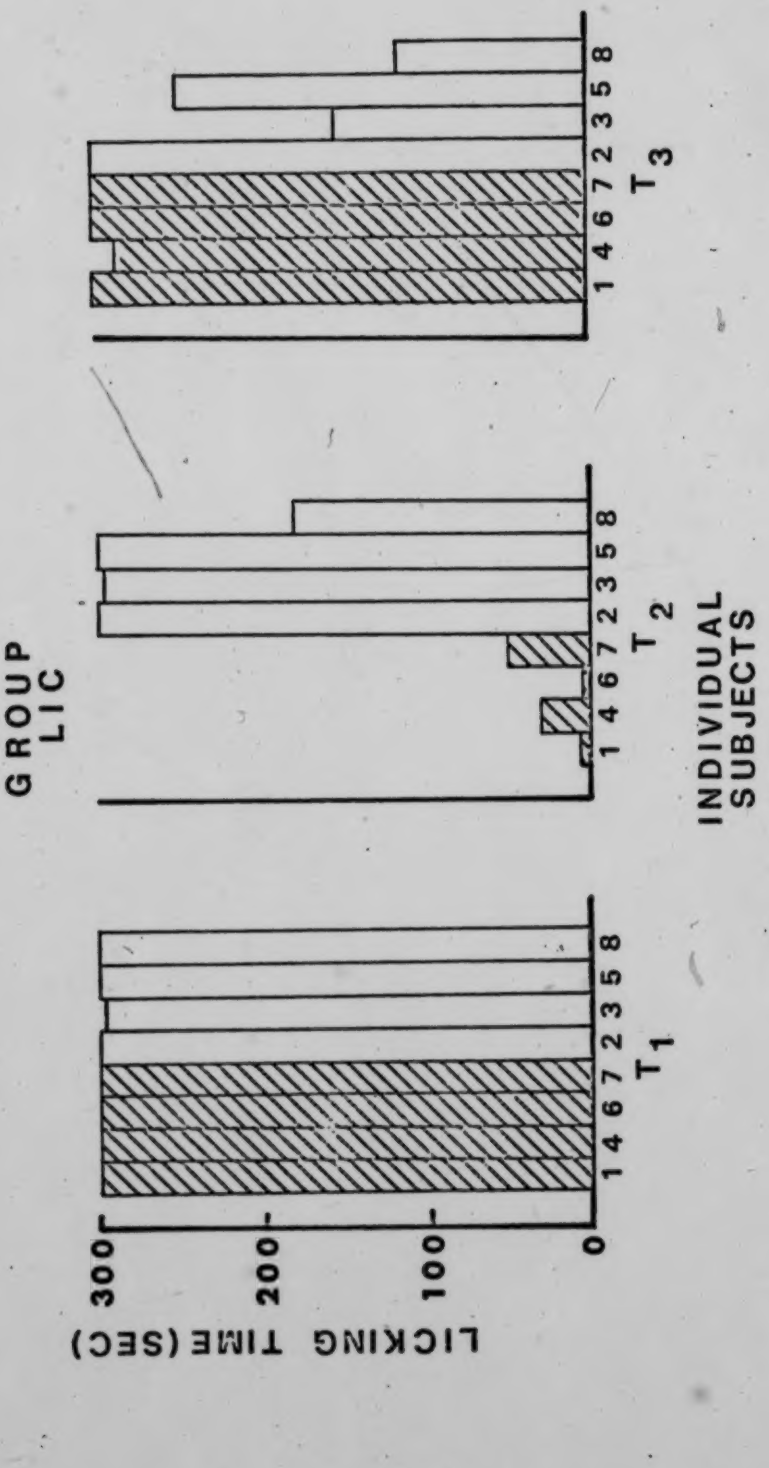
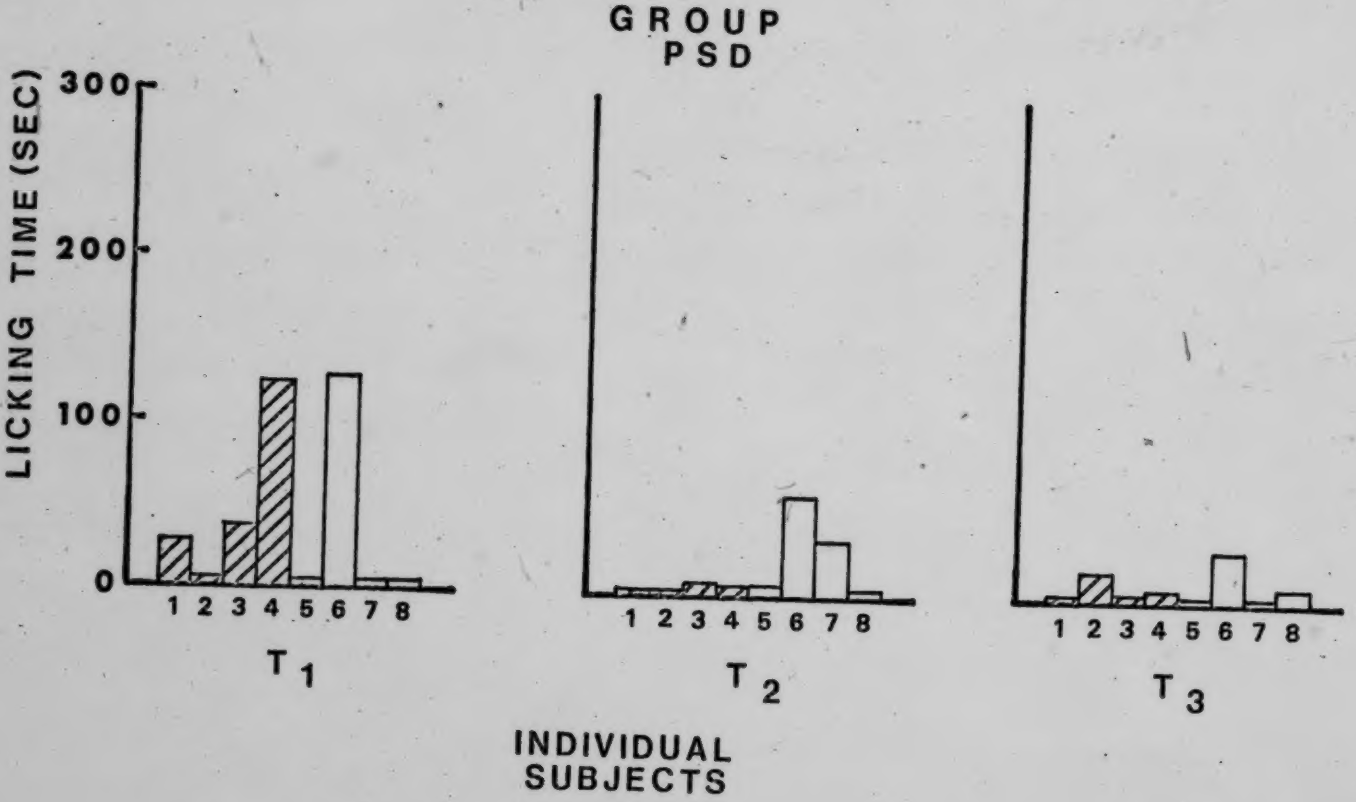
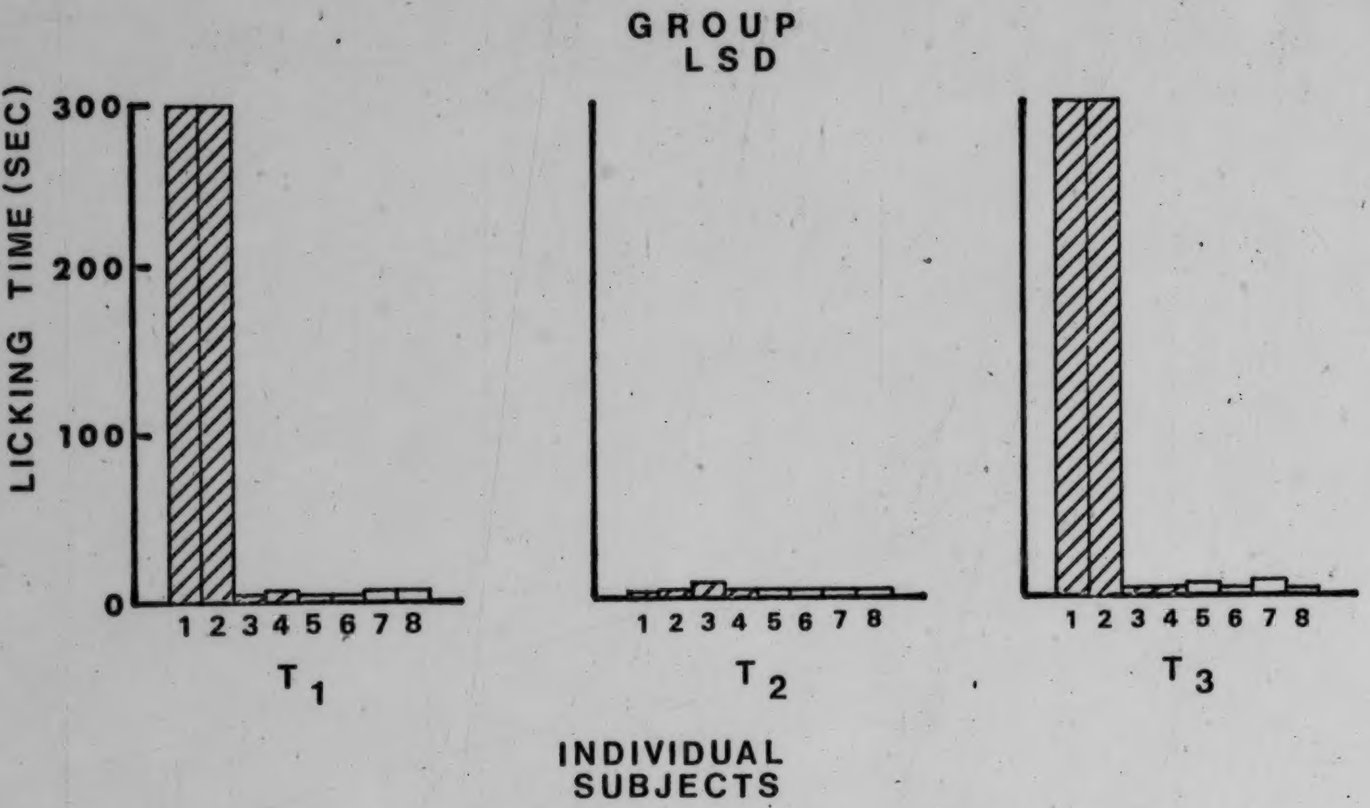
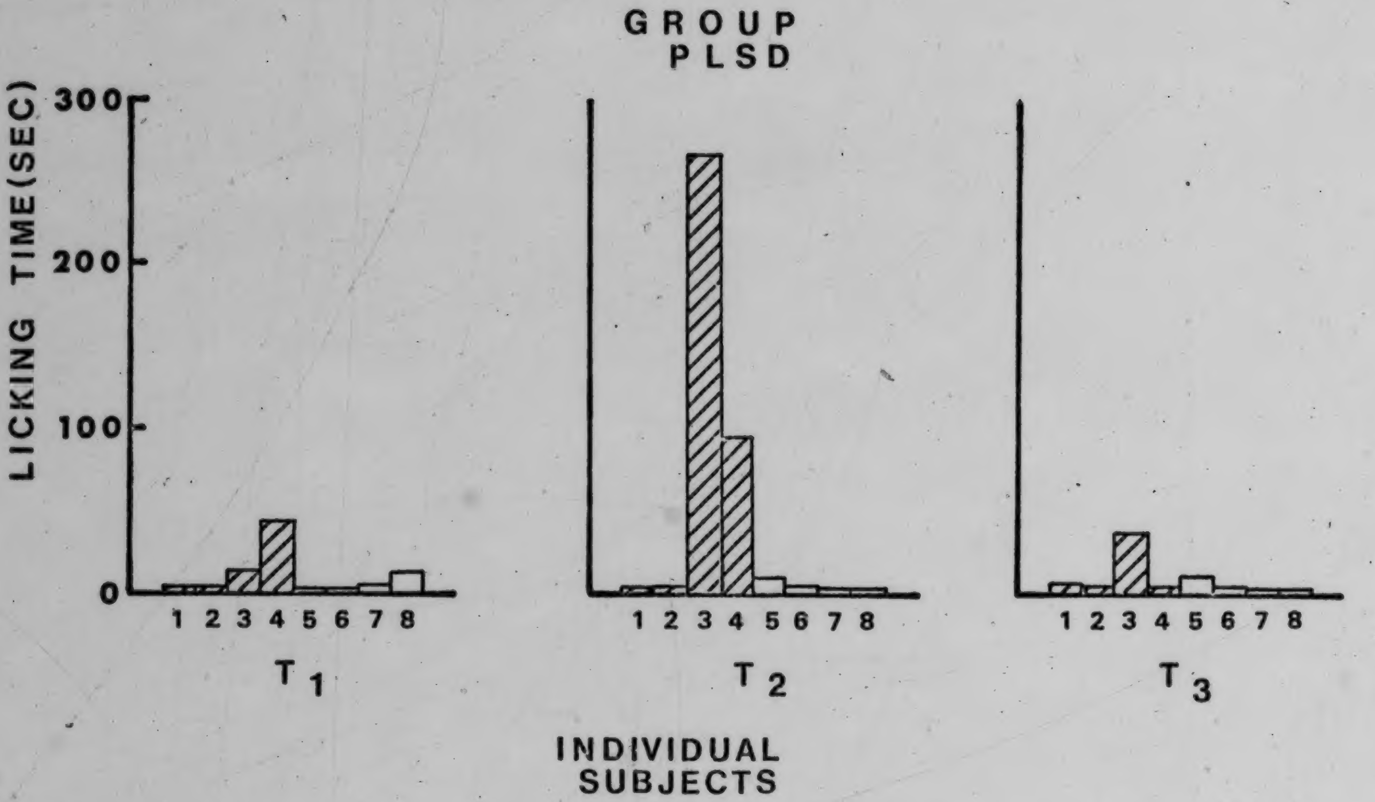
T_3
INDIVIDUAL
SUBJECTS


GROUP
LIC
LICKING TIME (SEC)
300
200
100
0
1 4 6 7 2 3 5 8
T1
1 4 6 7 2 3 5 8
T2
1 4 6 7 2 3 5 8
T3
INDIVIDUAL
SUBJECTS


GROUP
PSD
LICKING TIME (SEC)
300
200
100
0
1 2 3 4 5 6 7 8
T 1
1 2 3 4 5 6 7 8
T 2
1 2 3 4 5 6 7 8
T 3
INDIVIDUAL
SUBJECTS


GROUP
LSD
LICKING TIME (SEC)
300
200
100
0
1 2 3 4 5 6 7 8
T 1
1 2 3 4 5 6 7 8
T 2
1 2 3 4 5 6 7 8
T 3
INDIVIDUAL
SUBJECTS


GROUP
PLSD
LICKING TIME(SEC)
300
200
100
0
1 2 3 4 5 6 7 8
T 1
1 2 3 4 5 6 7 8
T 2
1 2 3 4 5 6 7 8
T 3
INDIVIDUAL
SUBJECTS